Supplementary material for the article:

Božinović, N.; Šegan, S.; Vojnovic, S.; Pavic, A.; Šolaja, B. A.; Nikodinovic-Runic, J.; Opsenica, I. M. Synthesis and Anti-Candida Activity of Novel Benzothiepino[3,2-c]Pyridine Derivatives. *Chemical Biology and Drug Design* **2016**, *88* (6), 795–806. https://doi.org/10.1111/cbdd.12809

Supporting Information

Synthesis and anti-*Candida* Activity of Novel Benzothiepino[3,2-*c*]pyridine Derivatives

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Table S2. Lethal and teratogenic effects observed in zebrafish (*Danio rerio*) embryos at different hours post fertilization (hpf).

Category	Developmental endpoints	Exposure time (hpf)			
		24	48	72	96
Lethal effect	Egg coagulation[a]	•	•	•	•
	No somite formation	•	•	•	•
	Tail not detached	•	•	•	•
	No heart-beat		•	•	•
Teratogenic effect	Malformation of head	•	•	•	•
	Malformation of eyes[b]	•	•	•	•
	Malformation of sacculi/otoliths[c]	•	•	•	•
	Malformation of chorda	•	•	•	•
	Malformation of tail[d]	•	•	•	•
	Scoliosis	•	•	•	•
	Heart beat frequency		•	•	•
	Blood circulation		•	•	•
	Pericardial edema	•	•	•	•
	Yolk edema	•	•	•	•
	Yolk deformation	•	•	•	•
	Growth retardation[e]	•	•	•	•

[a] No clear organs structure are recognized

[b] Malformation of eyes was recorded for the retardation in eye development and abnormality in shape and size.

[c] Presence of no, one or more than two otoliths per sacculus, as well as reduction and enlargement of otoliths and/or sacculi (otic vesicles).

[d] Tail malformation was recorded when the tail was bent, twisted or shorter than to control embryos as assessed by optical comparison.

[e] Growth retardation was recorded by comparing with the control embryos in development or size (before hatching, at 24 hpf and 48 hpf) or in a body length (after hatching, at and onwards 72 hpf) using by optical comparison using a inverted microscope (CKX41; Olympus, Tokyo, Japan)

Table S2. Effects of different concentrations of selected thiepines (**4**, **16** and **23**) and **voriconazole** on the development of zebrafish (*Danio re*rio) embryos assessed at 96 hours post fertilization (hpf).

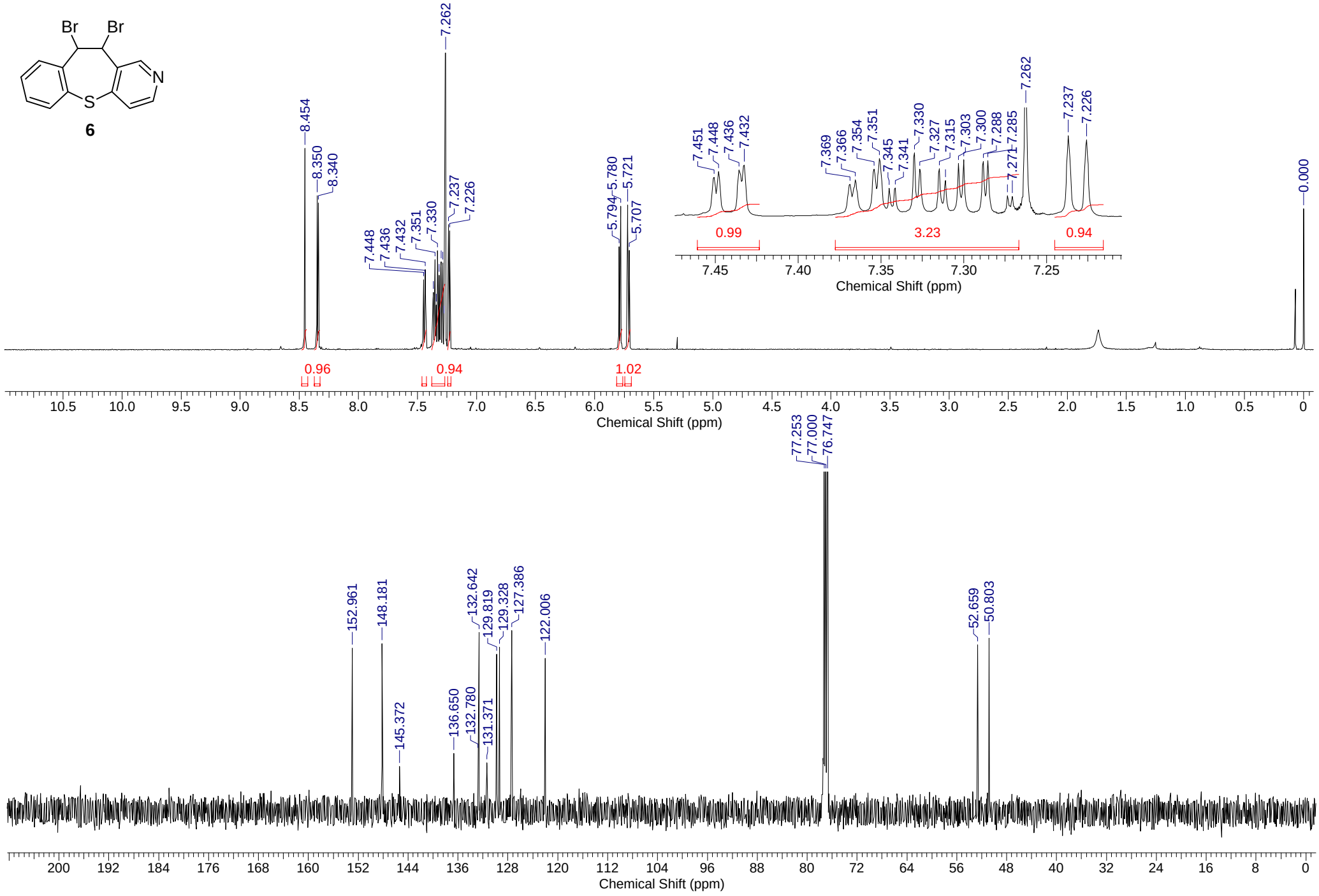
Compound concentration	Dead embryos[a]	Teratogenic embryos[a]	Normal embryos[a]	Growth retardation[b]	Notochord[b]	Eyes[b]	Otoliths[b]	Pericardial edema[b]	Yolk edema[b]	Heart beat[b]	Blood circulation[b]	Hatched[b]	Head malformation[c]	Skeletal deformities[c]	Tail tip[c]
4															
75 µg/ml	10.00	3.33	86.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	96.30	0.00	0.00	3.85
50 µg/ml	3.33	0.00	96.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	96.55	0.00	0.00	0.00
25 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
10 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
5 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
1 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
16															
75 µg/ml	20.00	80.00	0.00	100.00	0.00	97.92	0.00	52.08	0.00	0.00	0.00	100.00	100.00	97.92	100.00
50 µg/ml	6.67	1.67	86.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	1.89	1.89
25 µg/ml	0.00	1.67	98.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	1.67	0.00
10 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
5 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
1 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
23															
75 µg/ml	100.00	0.00	0.00												
50 µg/ml	33.33	61.67	5.00	0.00	0.00	92.50	0.00	87.50	0.00	0.00	0.00	42.50	100.00	100.00	100.00
25 µg/ml	20.00	53.33	26.67	0.00	0.00	66.67	0.00	58.33	0.00	0.00	0.00	100.00	66.67	50.00	66.67
10 µg/ml	3.33	5.00	91.67	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	5.17	0.00
5 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
1 µg/ml	0.00	0.00	100.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	100.00	0.00	0.00	0.00
Voriconazole															
75 µg/ml	100.00	0.00	0.00	-	-	-	-	-	-	-	-	-	-	-	-
50 µg/ml	100.00	0.00	0.00	-	-	-	-	-	-	-	-	-	-	-	-
25 µg/ml	100.00	0.00	0.00	-	-	-	-	-	-	-	-	-	-	-	-
10 µg/ml	80.00	20.00	0.00	100.00	0.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	0.00
5 µg/ml	36.67	63.33	0.00	100.00	0.00	100.00	100.00	100.00	0.00	0.00	0.00	100.00	100.00	94.74	0.00
1 µg/ml	20.00	60.00	20.00	20.00	100.00	44.44	0.00	55.56	0.00	0.00	0.00	100.00	100.00	55.56	0.00

Abrevitation used: (-) data not available due to 100% mortality.

[a] Percentage of mortality based on all eggs.

[b] Percentage of teratogenic effect based on all alive embryos at the time of assessment.

[c] Percentage of teratogenic effect based on all alive hatched embryos at the time of assessment.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7.237
7.226
5.794
5.780
5.721
5.707
0.96
0.94
1.02
0.000
7.451
7.448
7.436
7.432
7.369
7.366
7.354
7.351
7.345
7.341
7.330
7.327
7.315
7.303
7.300
7.288
7.285
7.271
7.262
7.237
7.226
0.99
3.23
0.94
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Chemical Shift (ppm)
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77.000
76.747
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145.372
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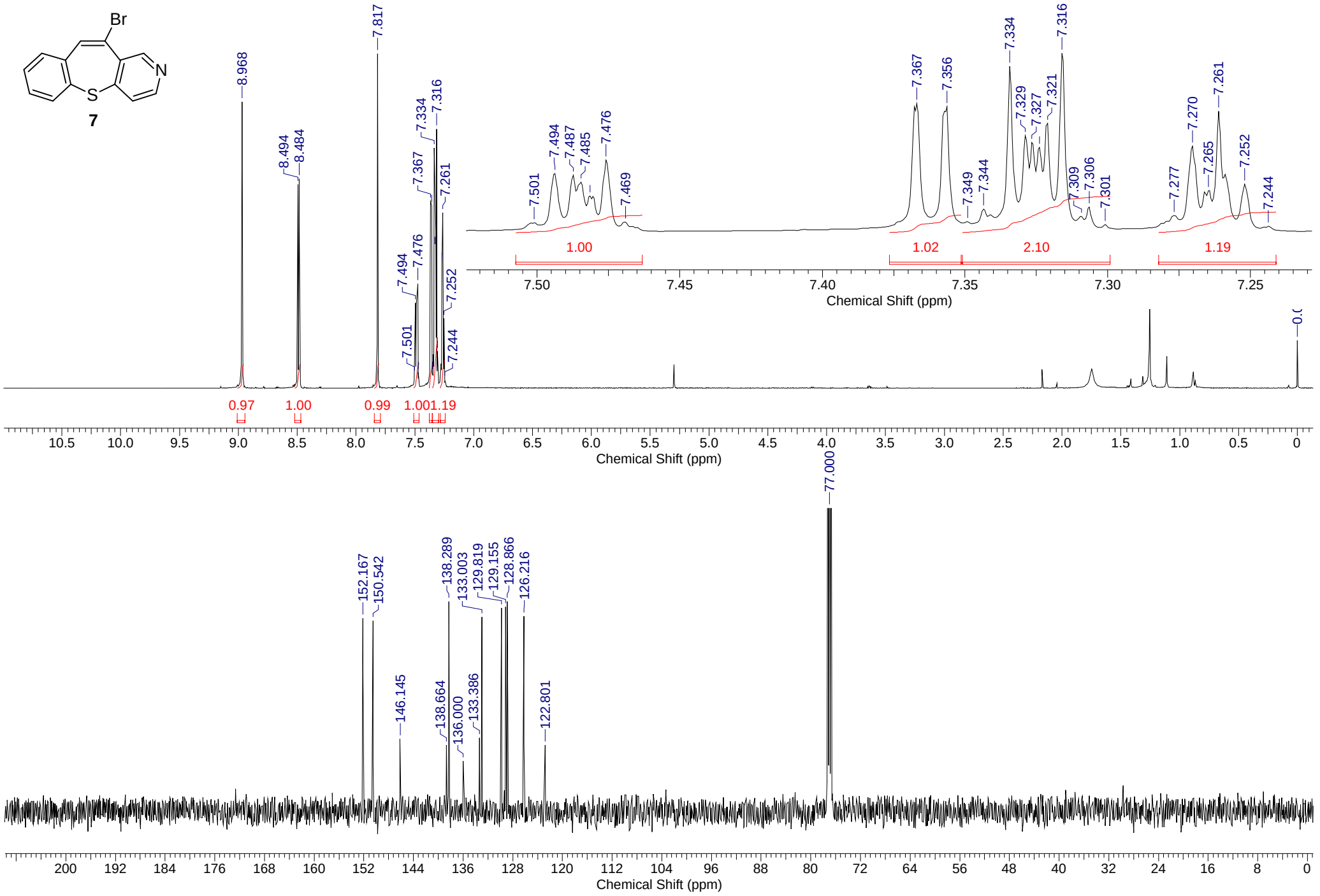
Chemical Shift (ppm)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7.356
7.349
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7.334
7.329
7.327
7.321
7.316
7.309
7.306
7.301
7.277
7.270
7.265
7.261
7.252
7.244
1.00
1.02
2.10
1.19
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0.97
1.00
0.99
1.00
1.19
Chemical Shift (ppm)
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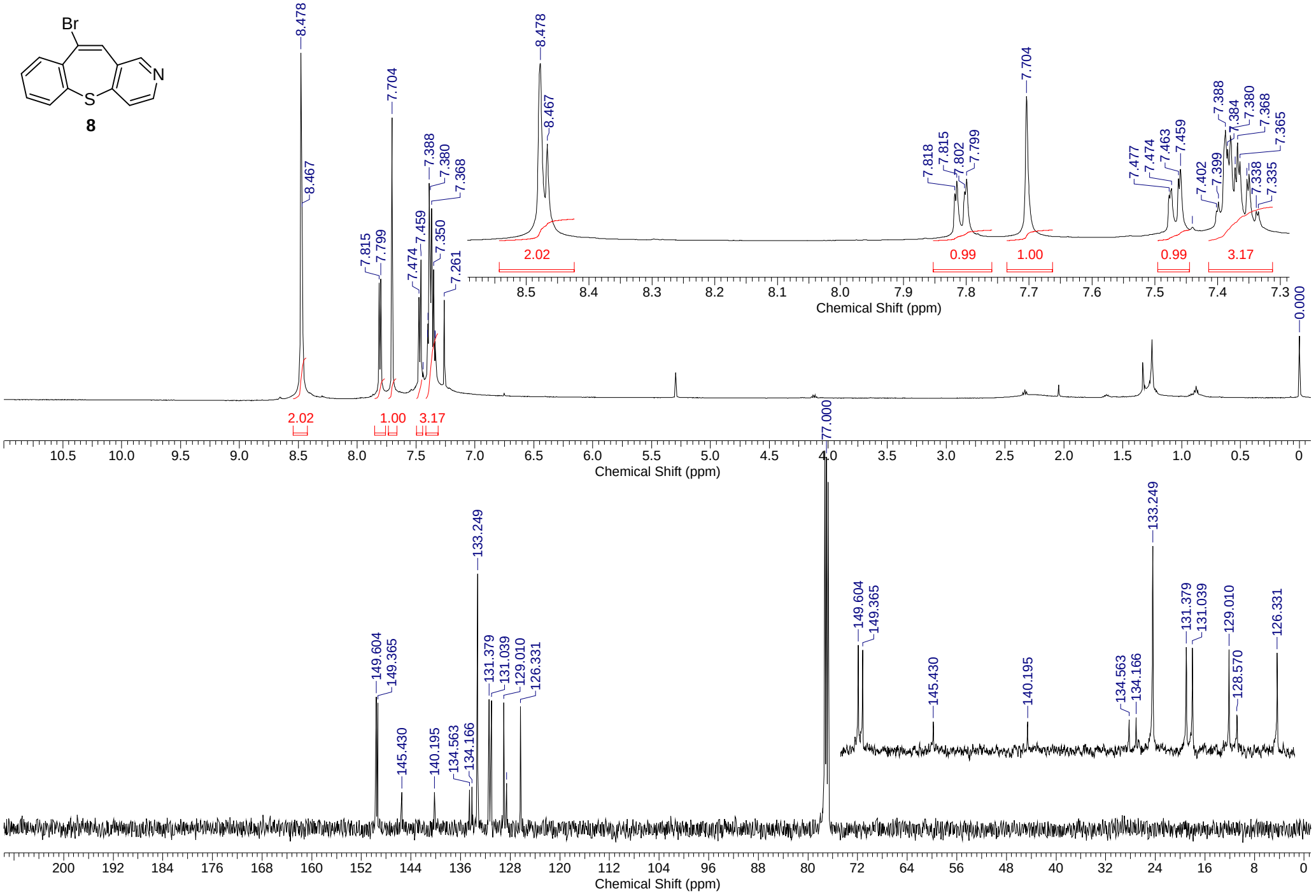
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7.477
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7.399
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7.338
7.335
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Chemical Shift (ppm)
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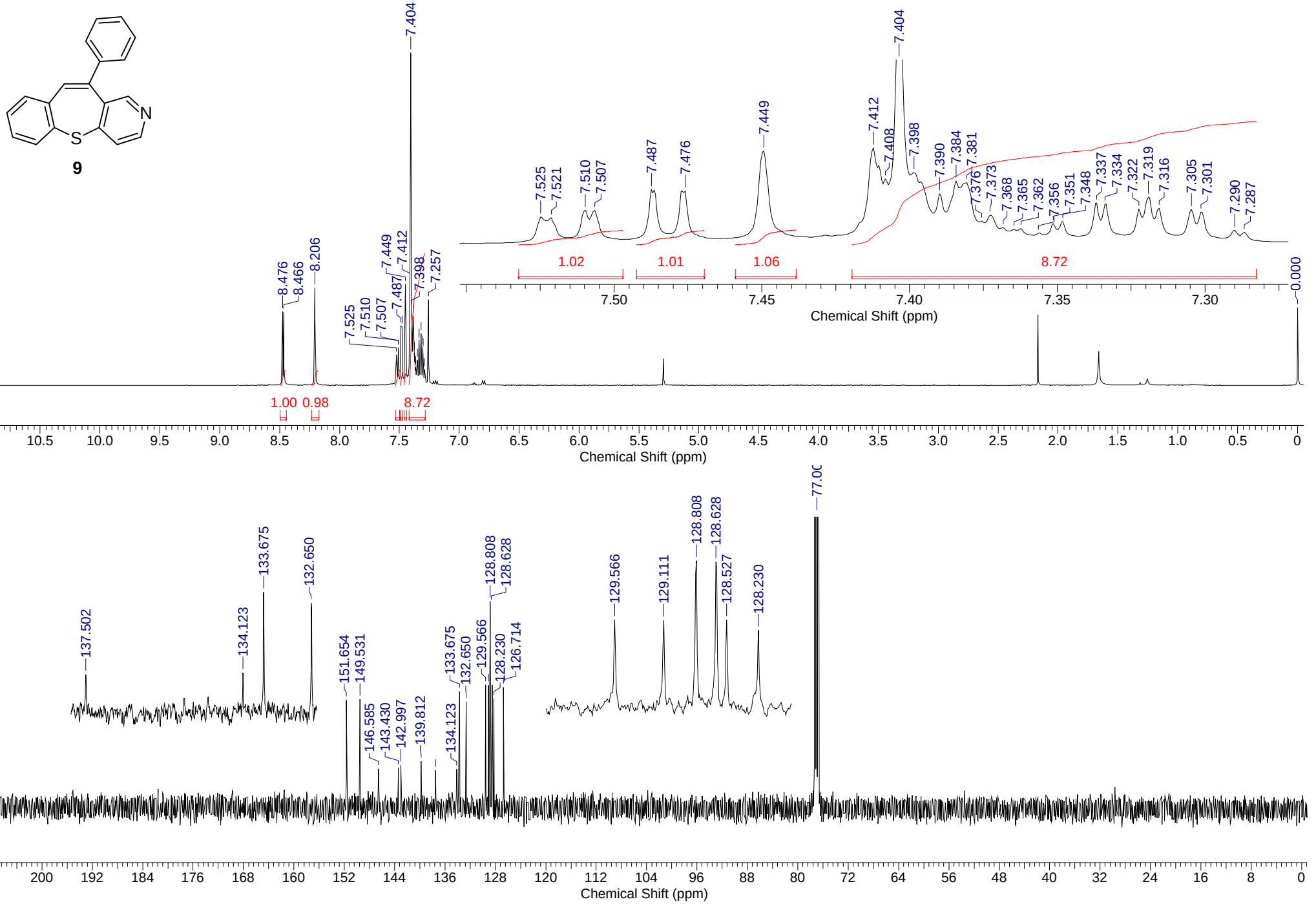
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7.408
7.404
7.398
7.390
7.384
7.381
7.376
7.373
7.368
7.365
7.362
7.356
7.351
7.348
7.337
7.334
7.322
7.319
7.316
7.305
7.301
7.290
7.287
7.257
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1.02
1.01
1.06
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151.654
149.531
146.585
143.430
142.997
139.812
134.123
133.675
132.650
129.566
128.808
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128.527
128.230
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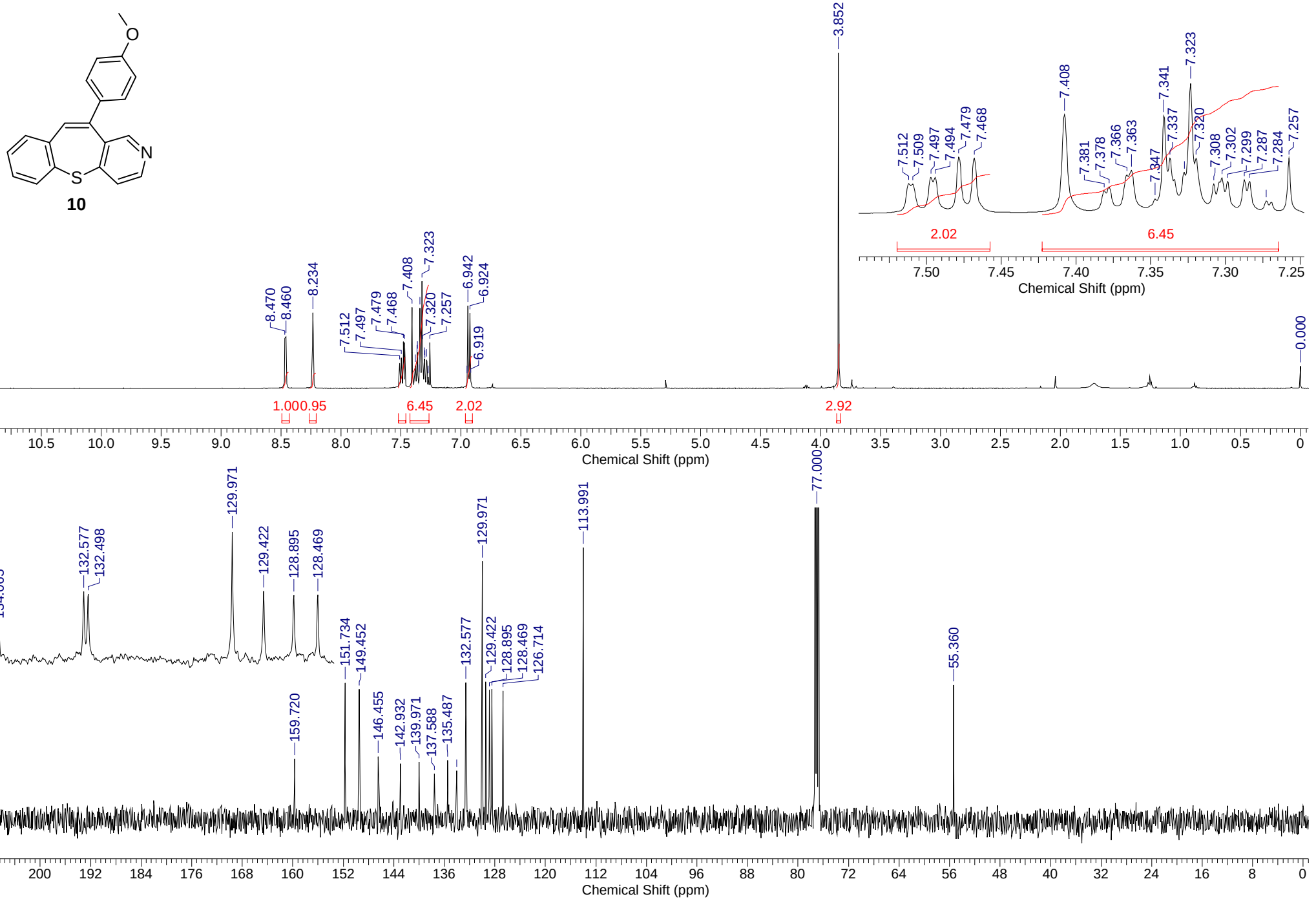
Chemical Shift (ppm)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7.347
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7.308
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139.971
137.588
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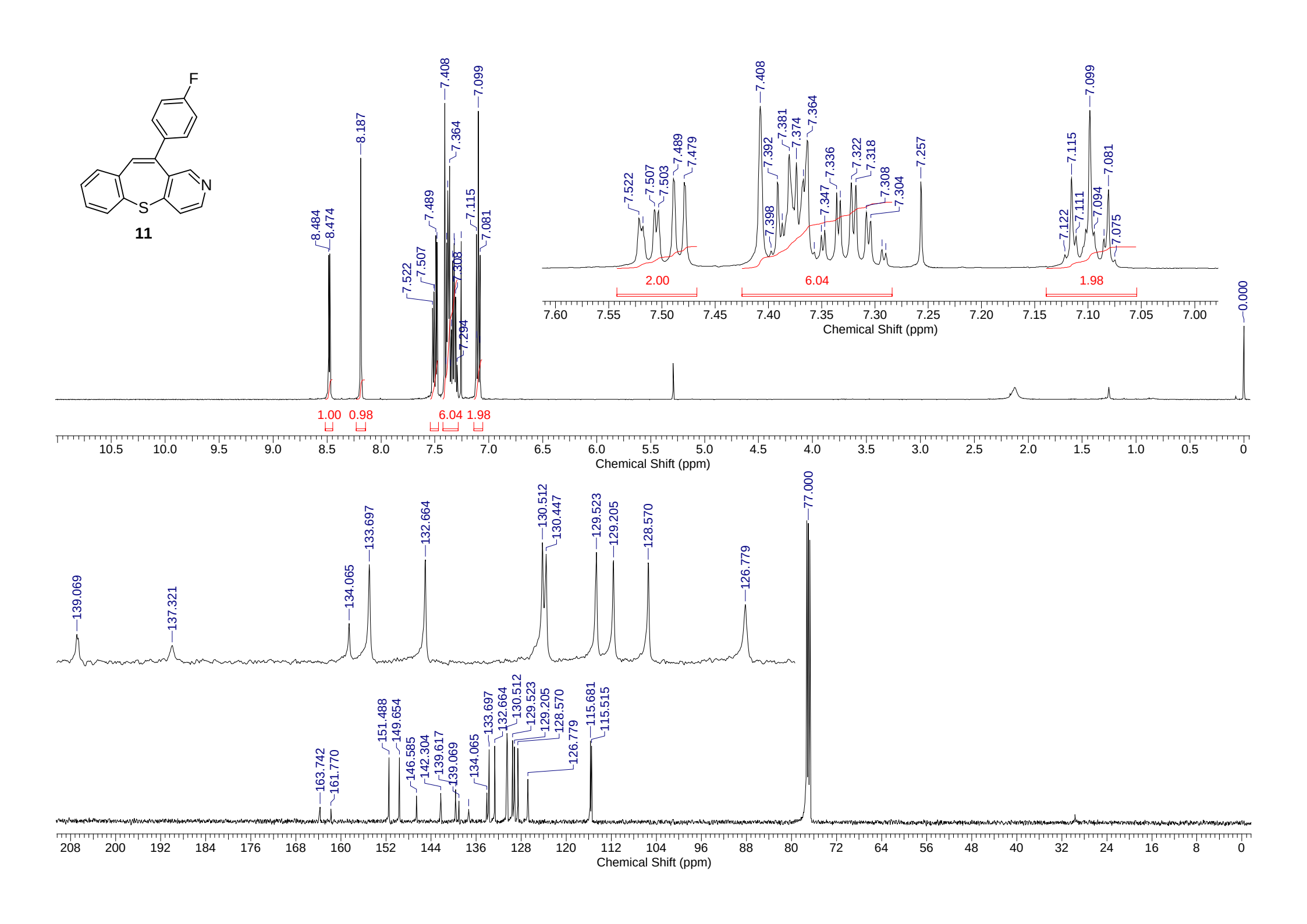
Chemical Shift (ppm)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7.081
1.00
0.98
6.04
1.98
Chemical Shift (ppm)
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7.503
7.489
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7.398
7.392
7.381
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7.122
7.115
7.111
7.099
7.094
7.081
7.075
2.00
6.04
1.98
Chemical Shift (ppm)
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137.321
134.065
133.697
132.664
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130.447
129.523
129.205
128.570
126.779
77.000
163.742
161.770
151.488
149.654
146.585
142.304
139.617
139.069
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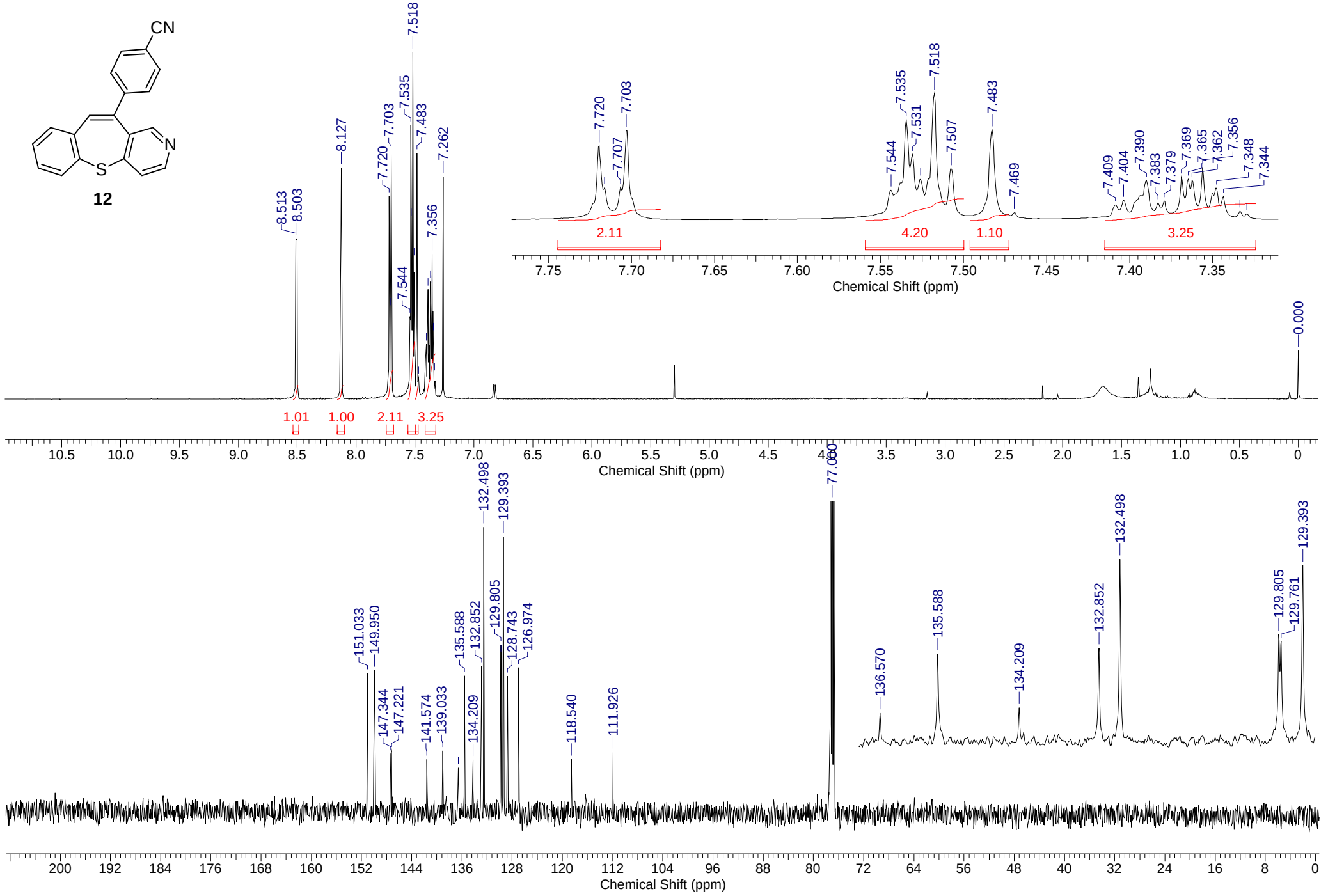
Chemical Shift (ppm)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1.01
1.00
2.11
3.25
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7.707
7.703
7.544
7.535
7.531
7.518
7.507
7.483
7.469
7.409
7.404
7.390
7.383
7.379
7.369
7.365
7.362
7.356
7.348
7.344
2.11
4.20
1.10
3.25
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147.221
141.574
139.033
135.588
134.209
132.852
132.498
129.805
129.393
128.743
126.974
118.540
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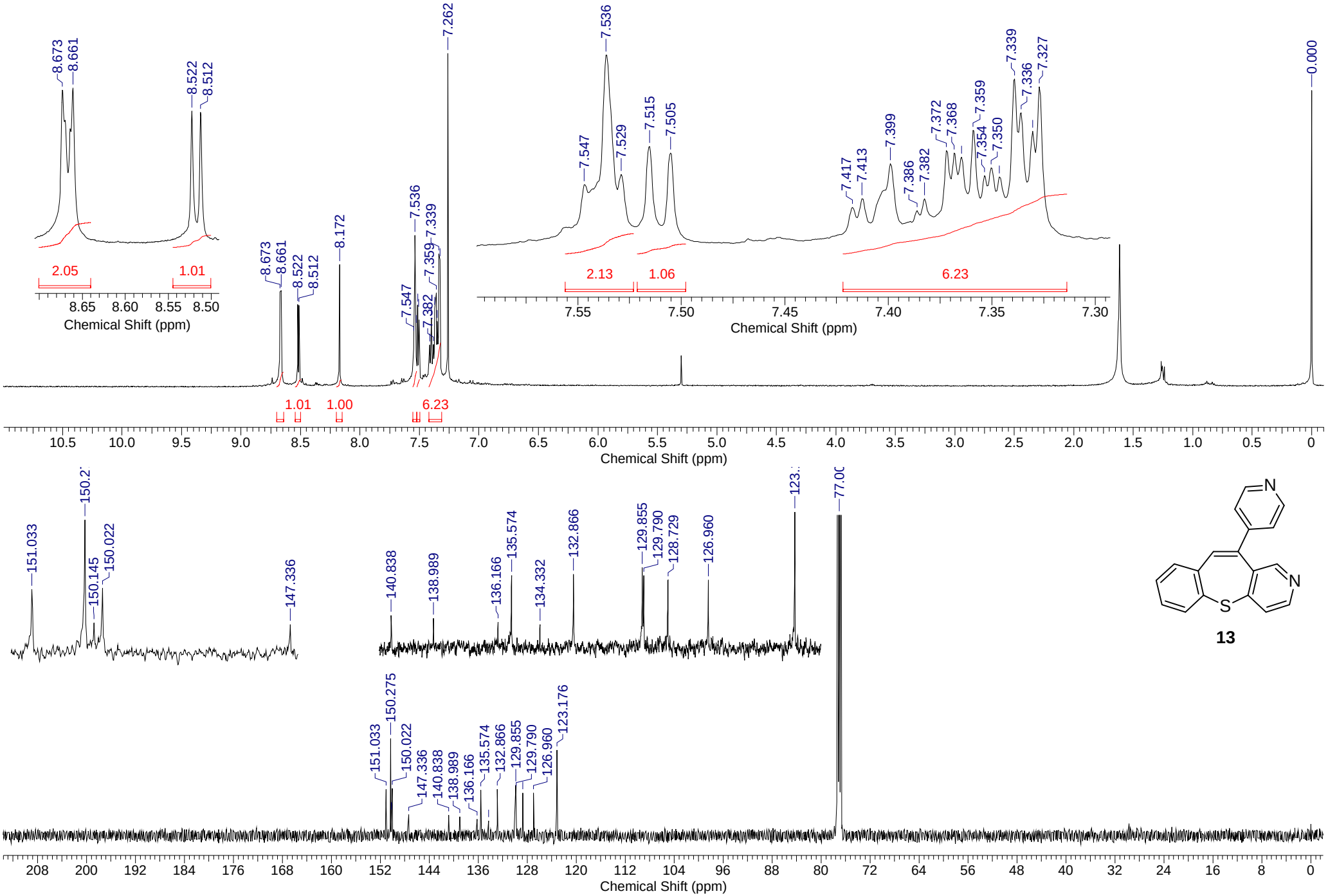
Chemical Shift (ppm)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7.339
7.336
7.327
7.262
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1.01
2.13
1.06
6.23
1.01
1.00
6.23
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S
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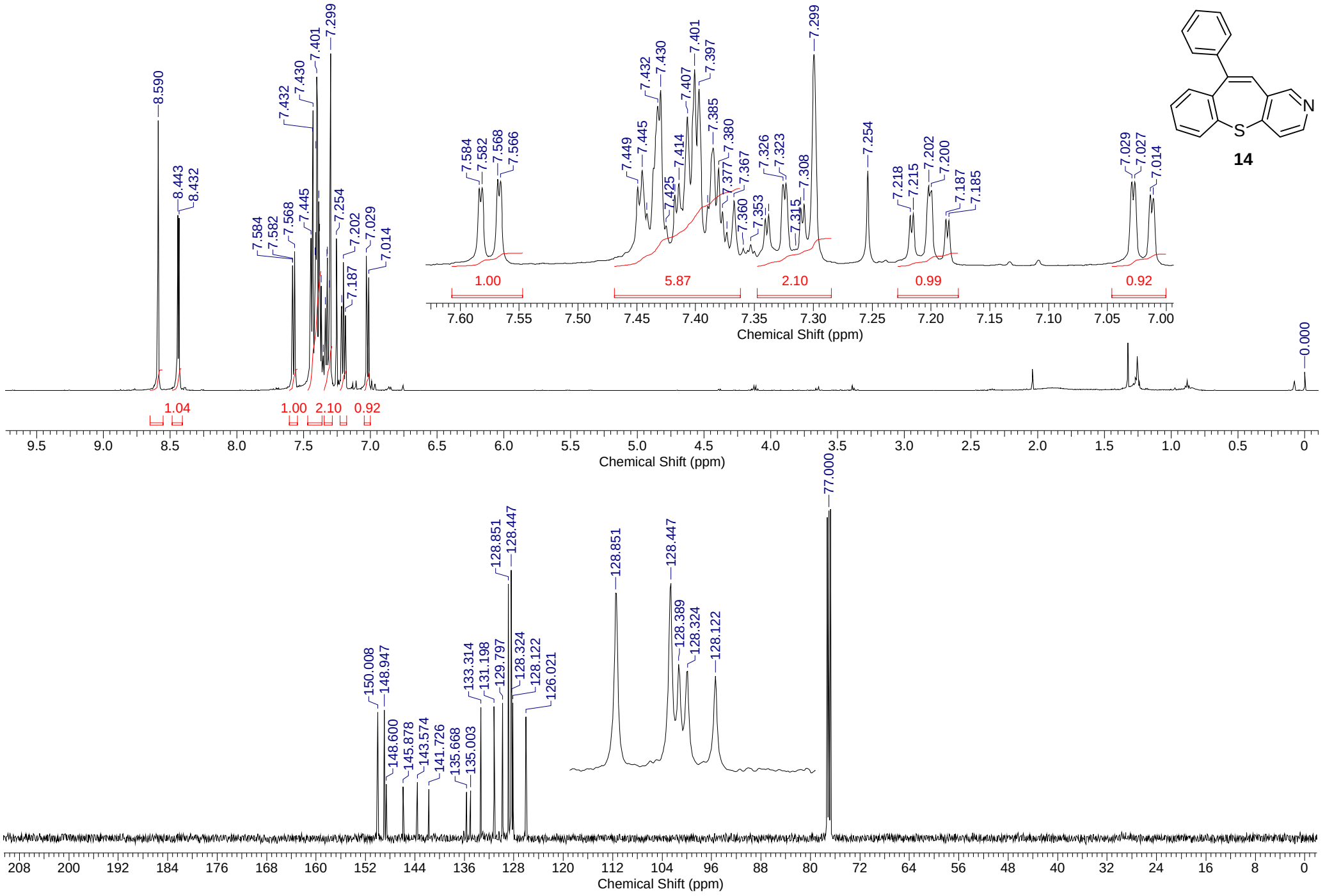
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7.432
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7.401
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7.254
7.202
7.187
7.029
7.014
1.04
1.00
2.10
0.92
Chemical Shift (ppm)
7.584
7.582
7.568
7.566
7.449
7.445
7.432
7.430
7.425
7.414
7.407
7.401
7.397
7.385
7.380
7.377
7.367
7.360
7.353
7.326
7.323
7.315
7.308
7.299
7.254
7.218
7.215
7.202
7.200
7.187
7.185
7.029
7.027
7.014
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5.87
2.10
0.99
0.92
Chemical Shift (ppm)
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N
S
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148.947
148.600
145.878
143.574
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131.198
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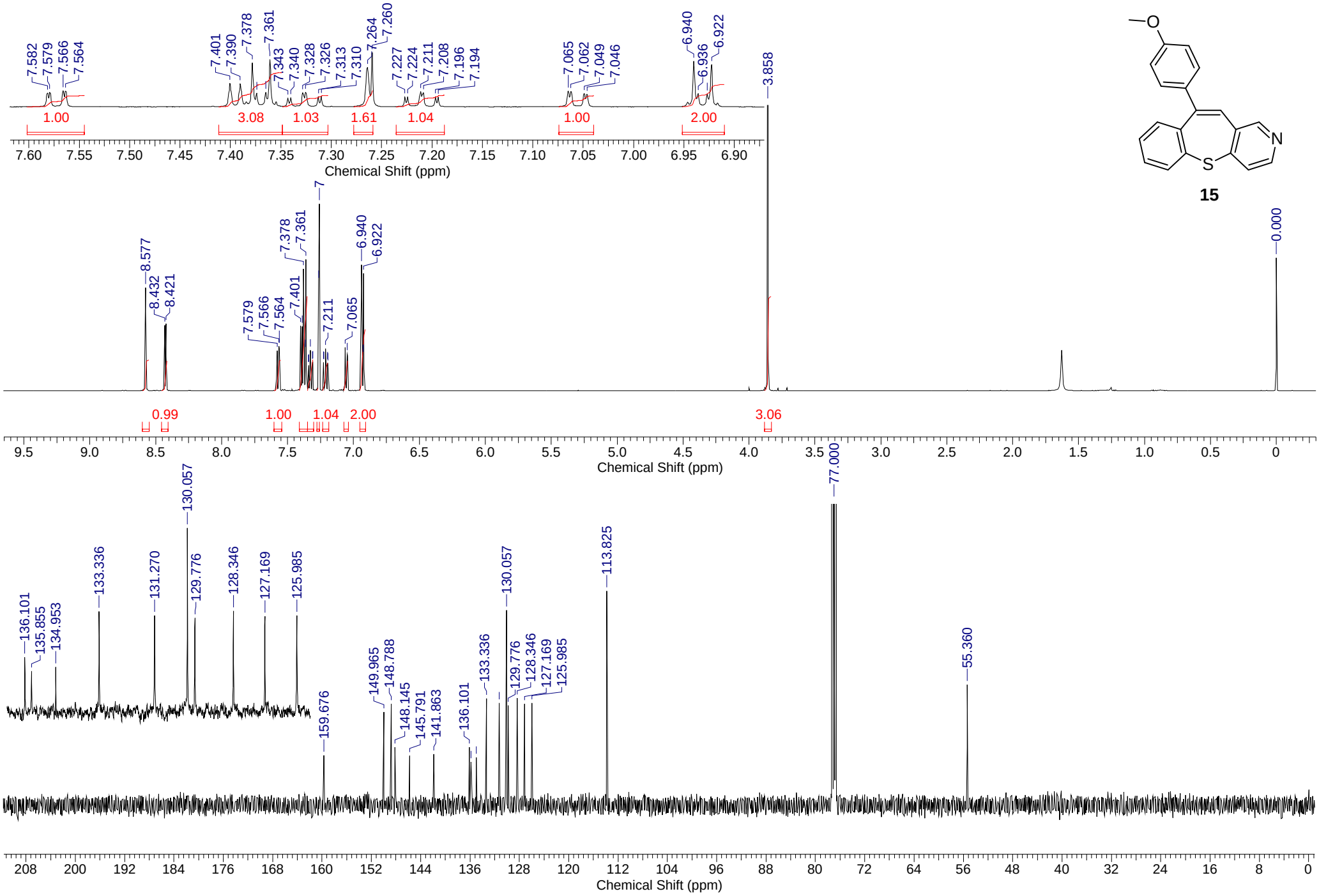
Chemical Shift (ppm)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7.313
7.310
7.264
7.260
7.227
7.224
7.211
7.208
7.196
7.194
7.065
7.062
7.049
7.046
6.940
6.936
6.922
3.858
1.00
3.08
1.03
1.61
1.04
1.00
2.00
Chemical Shift (ppm)
O
N
S
15
8.577
8.432
8.421
7.579
7.566
7.564
7.401
7.378
7.361
7.211
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1.00
1.04
2.00
3.06
Chemical Shift (ppm)
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135.855
134.953
133.336
131.270
130.057
129.776
128.346
127.169
125.985
159.676
149.965
148.788
148.145
145.791
141.863
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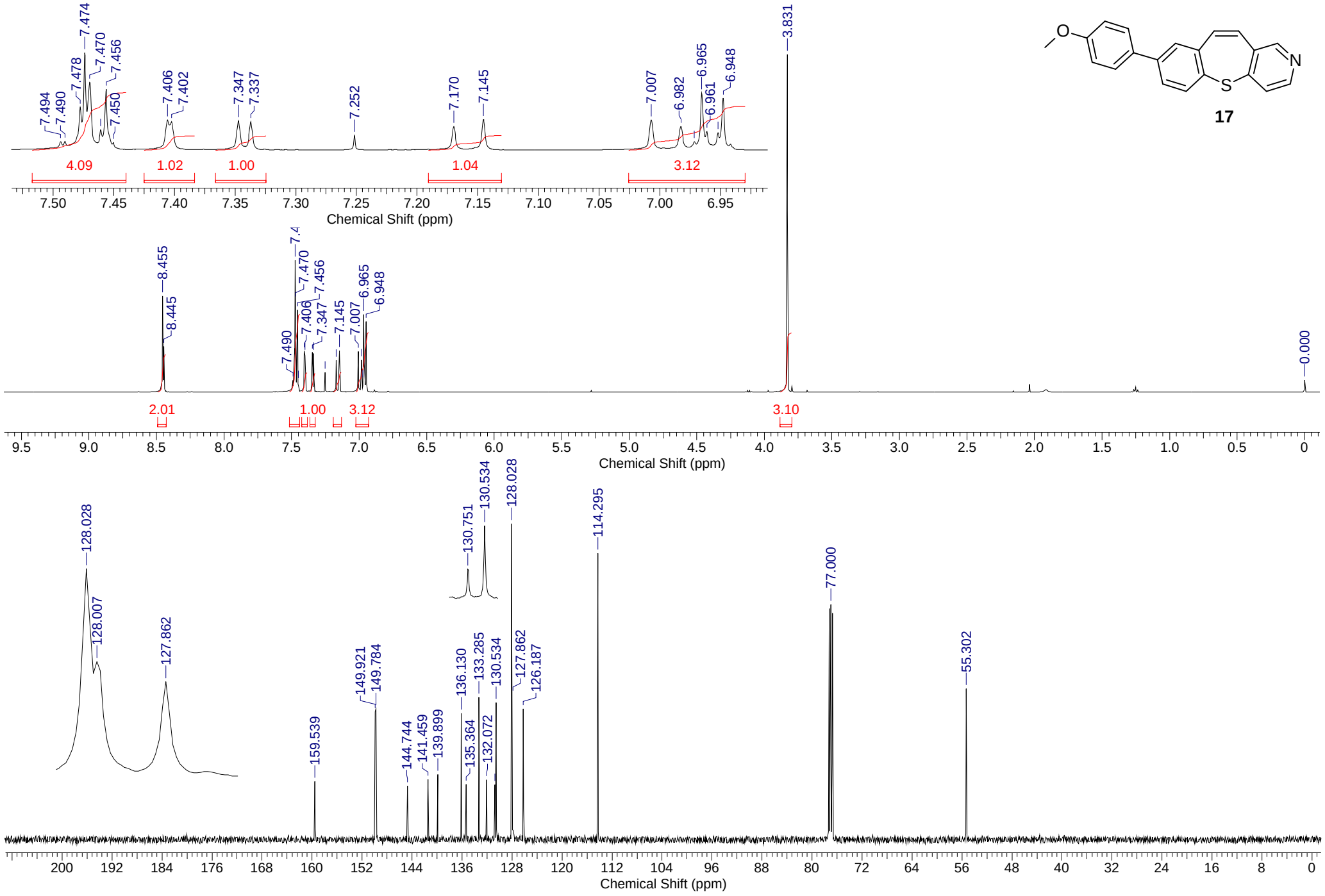
55.360
Chemical Shift (ppm)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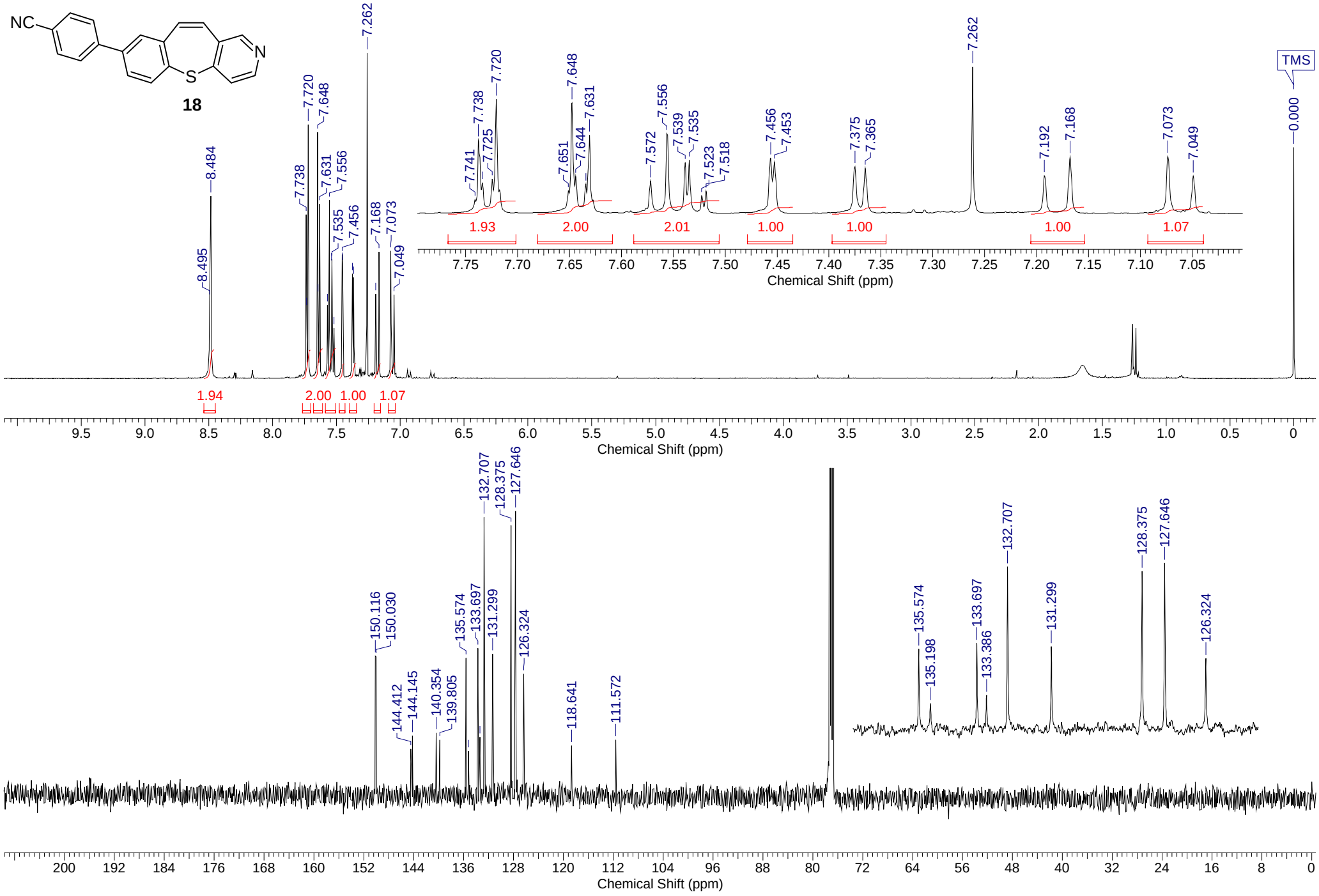
7.402
7.347
7.337
7.252
7.170
7.145
7.007
6.982
6.965
6.961
6.948
3.831
4.09
1.02
1.00
1.04
3.12
Chemical Shift (ppm)
8.455
8.445
7.490
7.470
7.456
7.406
7.347
7.145
7.007
6.965
6.948
0.000
2.01
1.00
3.12
3.10
Chemical Shift (ppm)
O
N
S
17
128.028
128.007
127.862
130.751
130.534
128.028
114.295
77.000
55.302
159.539
149.921
149.784
144.744
141.459
139.899
136.130
135.364
133.285
132.072
130.534
127.862
126.187
Chemical Shift (ppm)


NC
N
S
18
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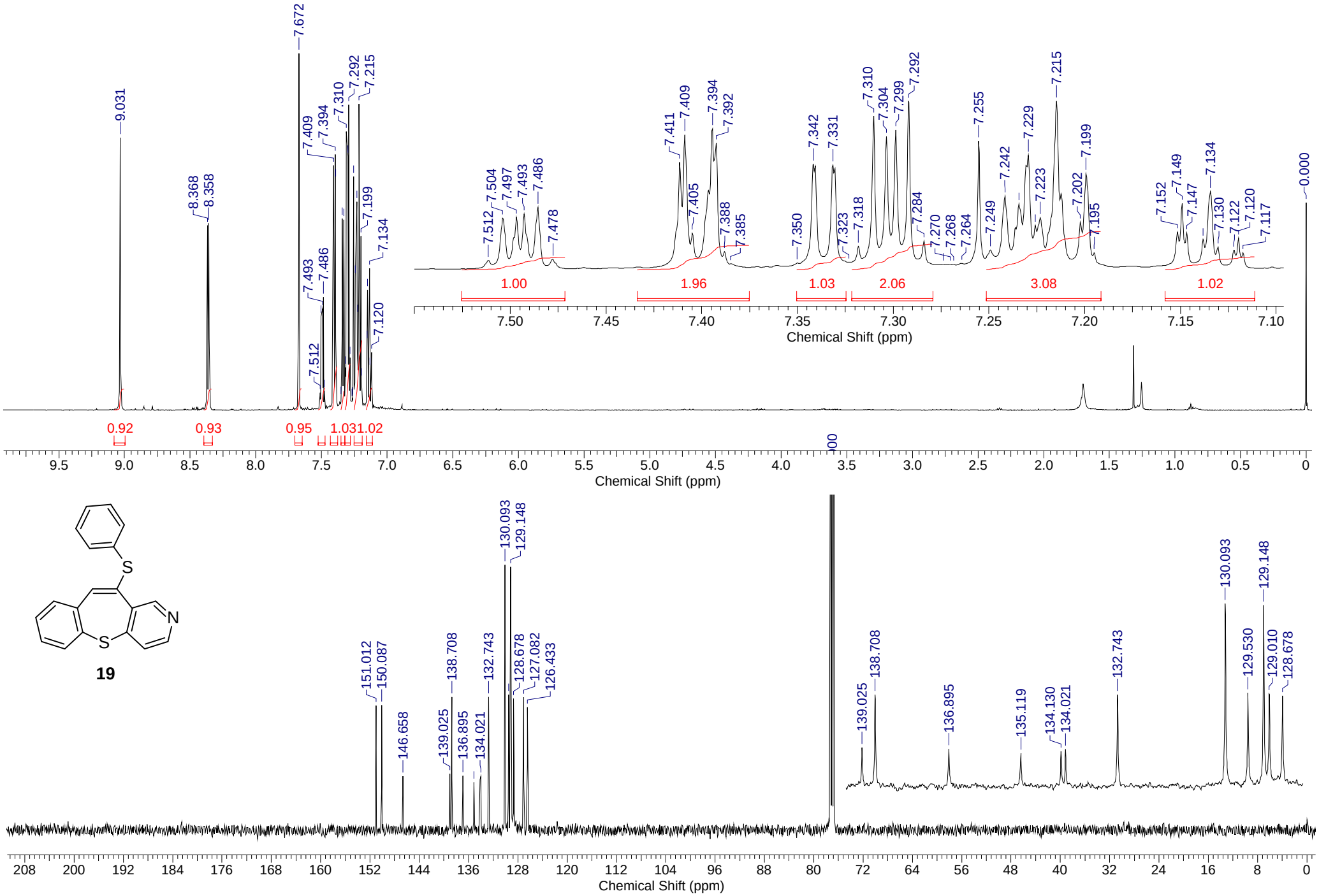
8.495
7.738
7.720
7.648
7.631
7.556
7.535
7.456
7.262
7.168
7.073
7.049
1.94
2.00
1.00
1.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)
7.741
7.738
7.725
7.720
7.651
7.648
7.644
7.631
7.572
7.556
7.539
7.535
7.523
7.518
7.456
7.453
7.375
7.365
7.262
7.192
7.168
7.073
7.049
1.93
2.00
2.01
1.00
1.00
1.00
1.07
7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05
Chemical Shift (ppm)
TMS
0.000
150.116
150.030
144.412
144.145
140.354
139.805
135.574
133.697
132.707
131.299
128.375
127.646
126.324
118.641
111.572
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)
135.574
135.198
133.697
133.386
132.707
131.299
128.375
127.646
126.324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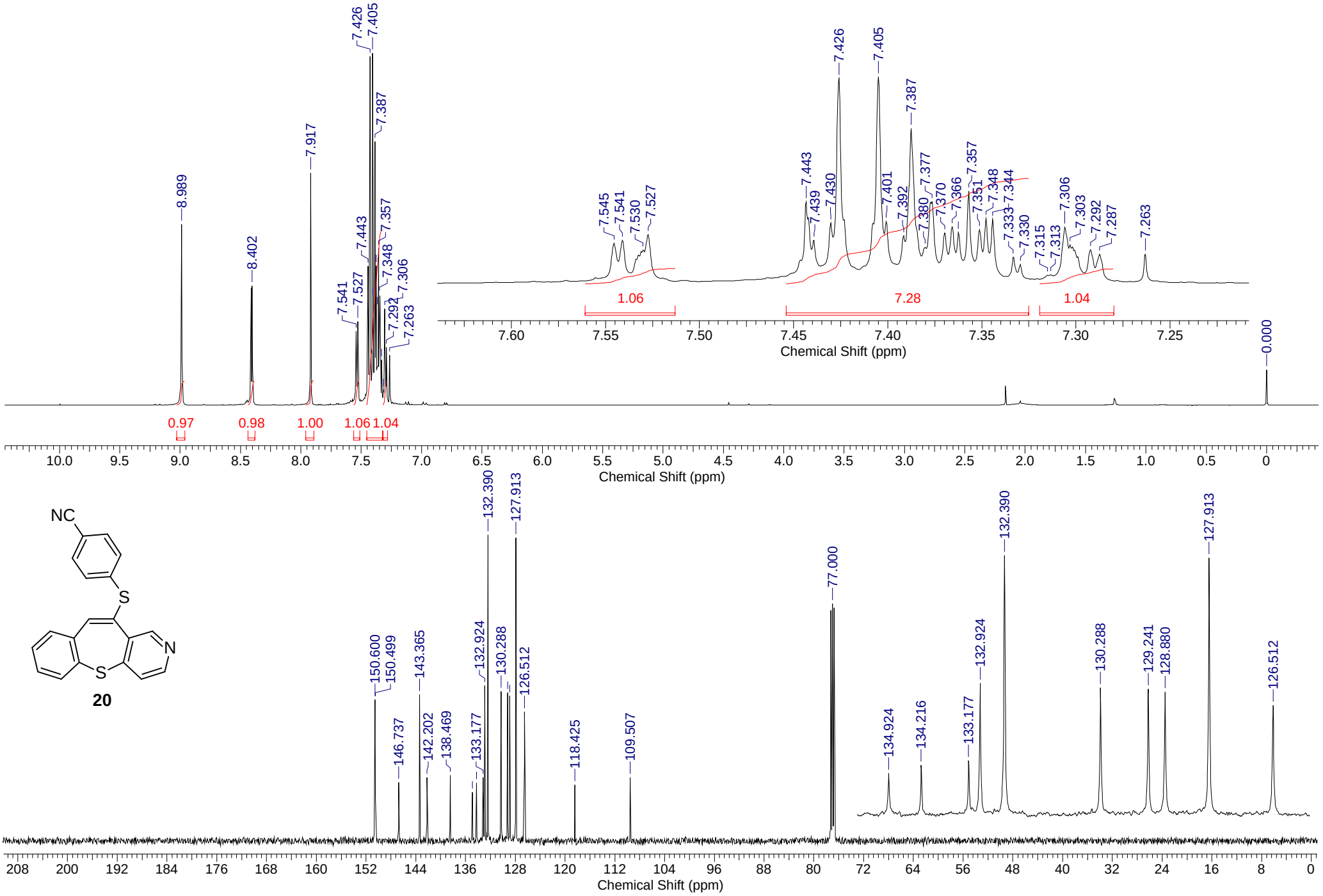
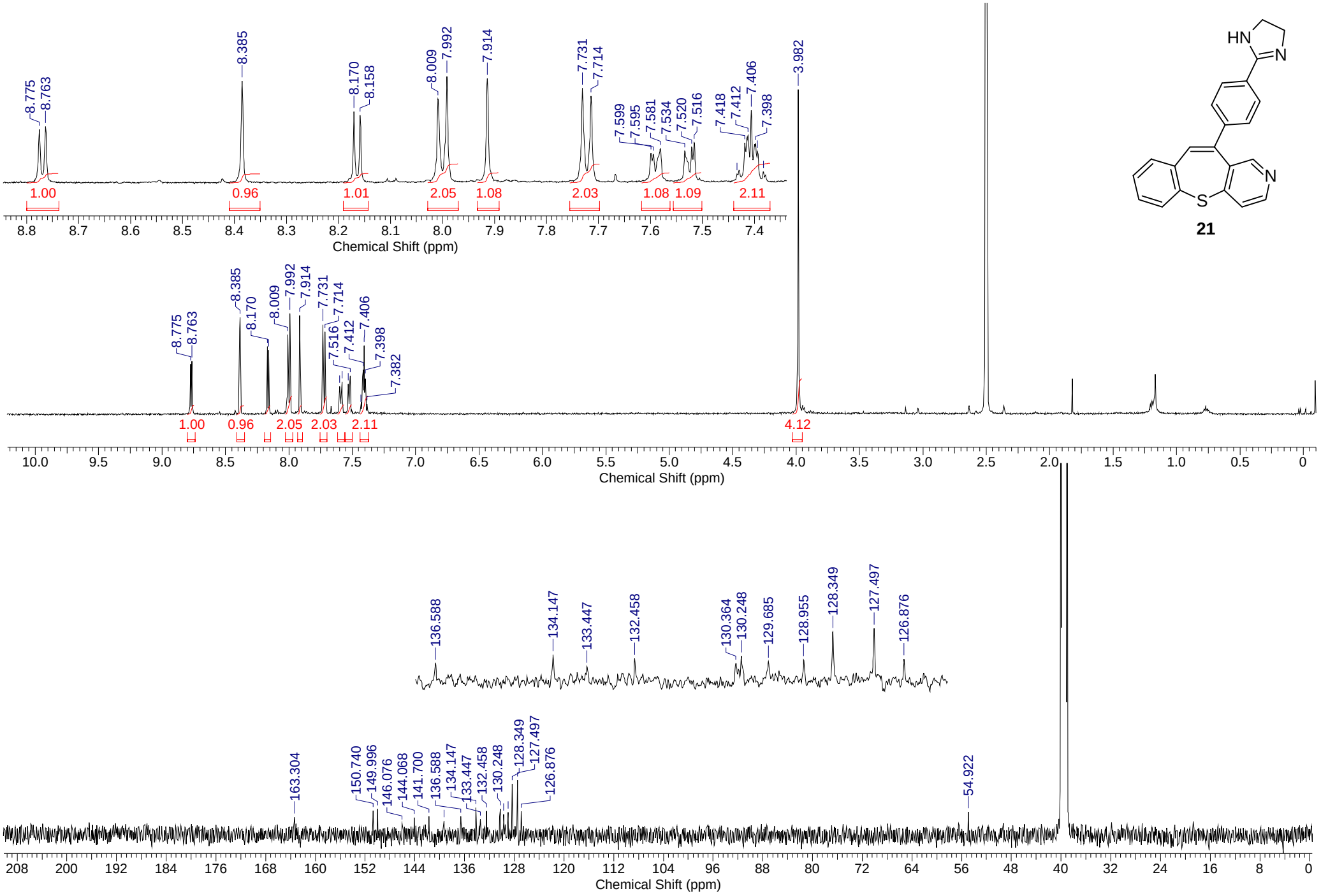
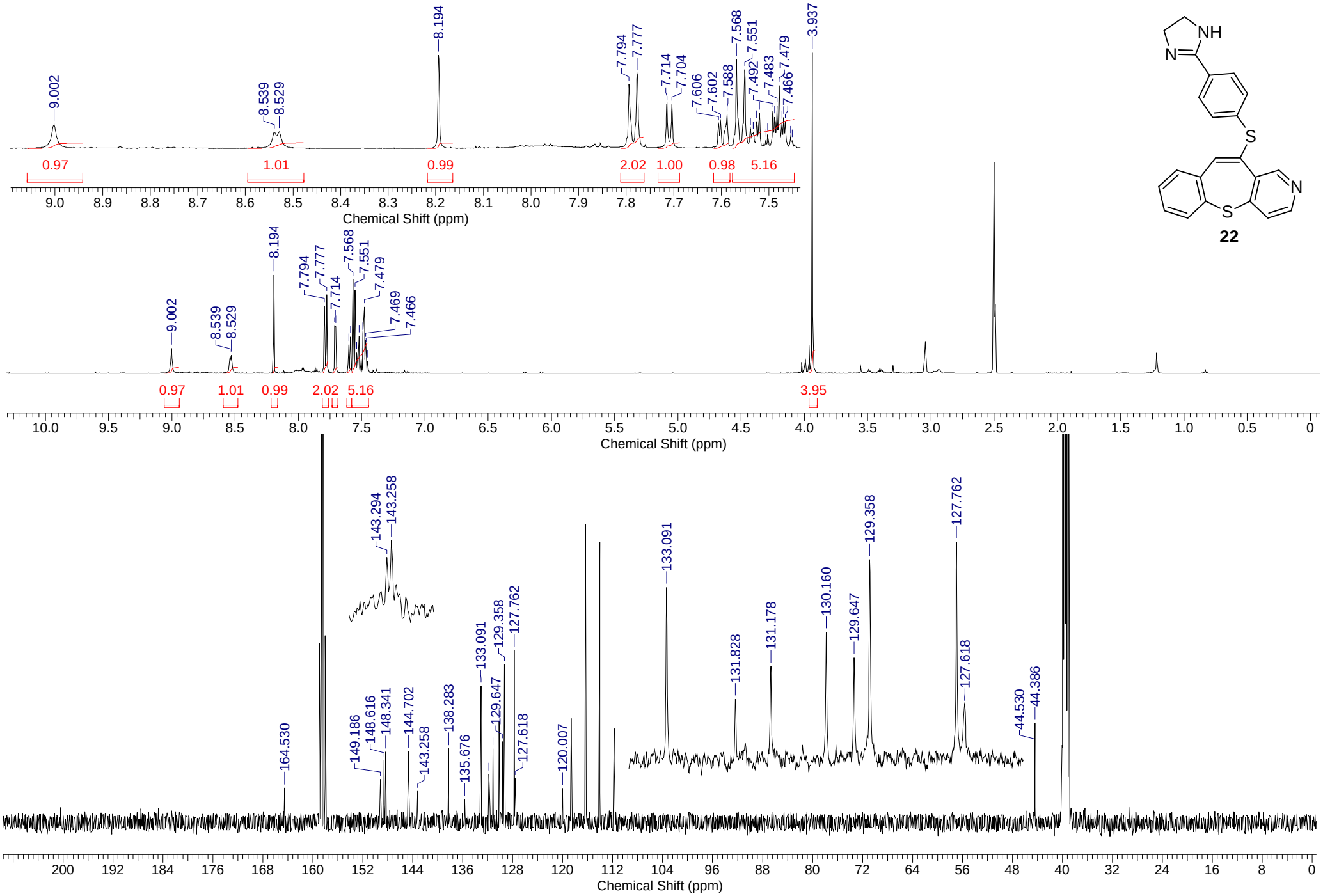
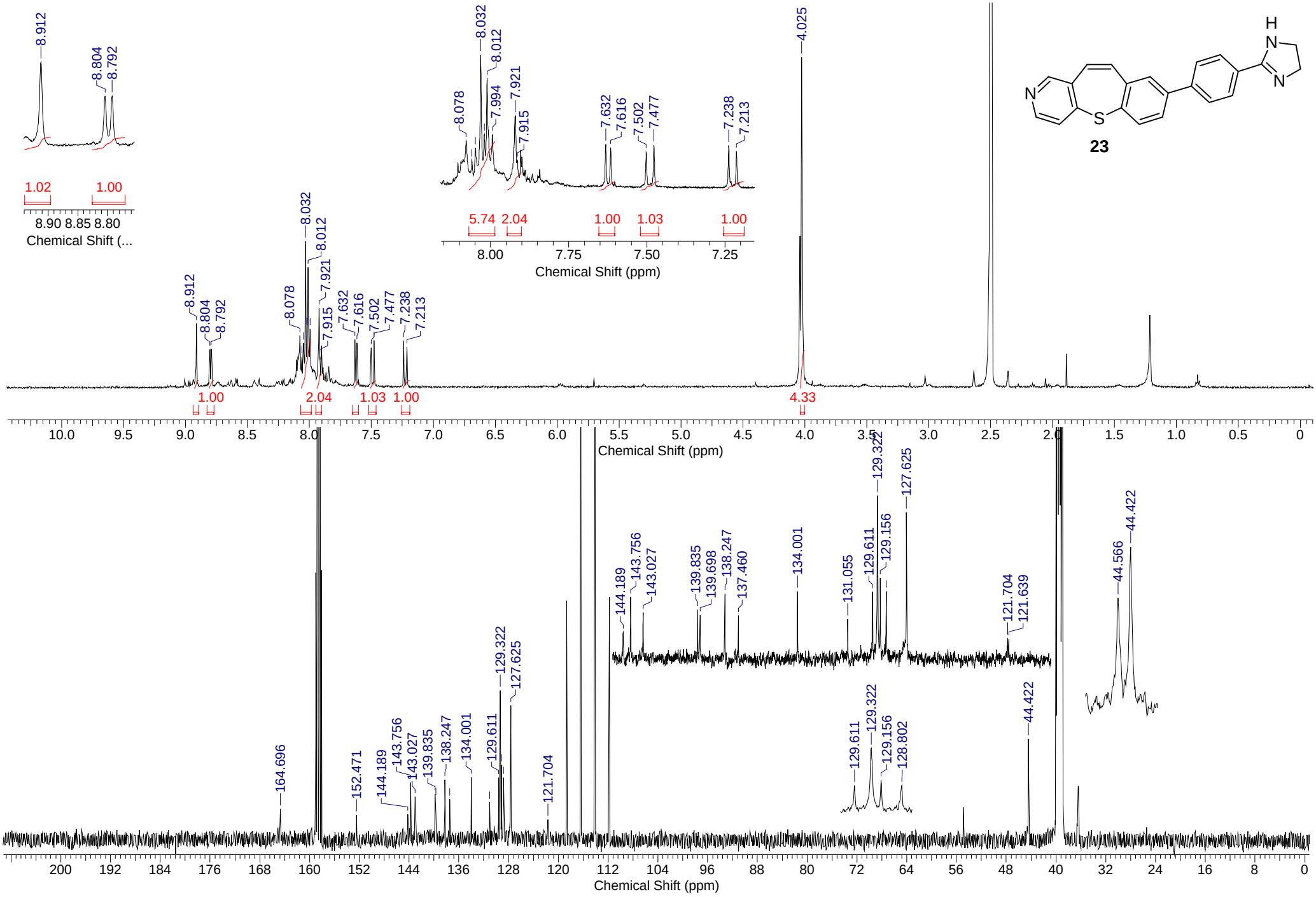
8.358
7.672
7.512
7.493
7.486
7.409
7.394
7.310
7.292
7.215
7.199
7.134
7.120
0.92
0.93
0.95
1.03
1.02
1.00
Chemical Shift (ppm)
7.512
7.504
7.497
7.493
7.486
7.478
7.411
7.409
7.405
7.394
7.392
7.388
7.385
7.350
7.342
7.331
7.323
7.318
7.310
7.304
7.299
7.292
7.284
7.270
7.268
7.264
7.255
7.249
7.242
7.229
7.223
7.215
7.202
7.199
7.195
7.152
7.149
7.147
7.134
7.130
7.122
7.120
7.117
0.000
1.00
1.96
1.03
2.06
3.08
1.02
Chemical Shift (ppm)
S
N
S
19
151.012
150.087
146.658
139.025
138.708
136.895
134.021
132.743
130.093
129.148
128.678
127.082
126.433
Chemical Shift (ppm)


8.989
8.402
7.917
7.426
7.405
7.387
7.443
7.357
7.348
7.306
7.541
7.527
7.294
7.263
0.97
0.98
1.00
1.06
1.04
Chemical Shift (ppm)
7.545
7.541
7.530
7.527
7.443
7.439
7.430
7.426
7.405
7.401
7.392
7.387
7.380
7.377
7.370
7.366
7.357
7.351
7.348
7.344
7.333
7.330
7.315
7.313
7.306
7.303
7.292
7.287
7.263
1.06
7.28
1.04
Chemical Shift (ppm)
0.000
NC
S
N
S
20
150.600
150.499
146.737
143.365
142.202
138.469
133.177
132.924
132.390
130.288
127.913
126.512
118.425
109.507
77.000
134.924
134.216
133.177
132.924
132.390
130.288
129.241
128.880
127.913
126.512
Chemical Shift (ppm)


8.775
8.763
8.385
8.170
8.158
8.009
7.992
7.914
7.731
7.714
7.599
7.595
7.581
7.534
7.520
7.516
7.418
7.412
7.406
7.398
3.982
1.00
0.96
1.01
2.05
1.08
2.03
1.08
1.09
2.11
Chemical Shift (ppm)
8.775
8.763
8.385
8.170
8.009
7.992
7.914
7.731
7.714
7.516
7.412
7.406
7.398
7.382
1.00
0.96
2.05
2.03
2.11
4.12
Chemical Shift (ppm)
136.588
134.147
133.447
132.458
130.364
130.248
129.685
128.955
128.349
127.497
126.876
163.304
150.740
149.996
146.076
144.068
141.700
136.588
134.147
133.447
132.458
130.248
128.349
127.497
126.876
54.922
Chemical Shift (ppm)
HN
N
N
S
21


9.002
8.539
8.529
8.194
7.794
7.777
7.714
7.704
7.606
7.602
7.588
7.568
7.551
7.492
7.483
7.479
7.466
3.937
0.97
1.01
0.99
2.02
1.00
0.98
5.16
3.95
Chemical Shift (ppm)
NH
N
S
S
N
22
143.294
143.258
164.530
149.186
148.616
148.341
144.702
143.258
138.283
135.676
133.091
129.647
129.358
127.762
127.618
120.007
131.828
131.178
130.160
129.647
129.358
127.762
127.618
44.530
44.386


8.912
8.804
8.792
1.02
1.00
8.90 8.85 8.80
Chemical Shift (...
8.032
8.012
8.078
7.994
7.921
7.915
7.632
7.616
7.502
7.477
7.238
7.213
5.74
2.04
1.00
1.03
1.00
8.00
7.75
7.50
7.25
Chemical Shift (ppm)
4.025
4.33
H
N
N
N
S
23
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)
164.696
152.471
144.189
143.756
143.027
139.835
138.247
134.001
129.611
129.322
127.625
121.704
131.055
129.156
137.460
121.639
44.566
44.422
128.802
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

HPLC analyses for purity

The HPLC analyses were performed in diverse systems:

Method A

Zorbax Eclipse Plus C18 4.6 x 150 mm, 1.8 µ, S.N. USWKY01594 was used as the stationary phase. The eluent was made from the following solvents: 0.2 % formic acid in water (A) and acetonitrile (B). The analysis were performed at the UV max of the compounds (at 270 nm or 300 nm) to maximize selectivity. The compounds were dissolved in dichloromethane or methanol; the final concentrations were ≈ 1 mg ml^{-1}; the flow rate was 0.5 ml min^{-1}.

Compounds **7**, **9**, **10**, **11**, **12** and **19** were eluted using the gradient protocol: 0 – 0.5 min 95 % A, 0.5 - 3 min 95 % A → 5 % A, 3 - 13 min 5 % A, 13 – 14 min 5 % A → 95 % A, 14 – 16 min 95 % A.

Compound **21** was eluted using the gradient protocol: 0 – 0.5 min 95 % A, 0.5 - 3 min 95 % A → 5 % A, 3 - 13 min 5 % A, 13 – 14 min 5 % A → 95 % A, 14 – 16 min 95 % A.

Method B

Zorbax Eclipse XDB-C18 4.6 x 50 mm, 1.8 µ, S.N. USWDY02826 was used as the stationary phase. The eluent was made from the following solvents: 0.2 % formic acid in water (A) and acetonitrile (B). The analysis were performed at the UV max of the compounds (at 270 nm or 300 nm) to maximize selectivity. The compounds were dissolved in dichloromethane or methanol; the final concentrations were ≈ 1 mg ml^{-1}; the flow rate was 0.5 ml min^{-1}.

Compounds **7**, **9**, **10**, **11**, **12, 19** and **21** were eluted using the gradient protocol: 0 – 0.5 min 95 % A, 0.5 - 3 min 95 % A → 5 % A, 3 - 13 min 5 % A, 13 – 14 min 5 % A→ 95 % A, 14 – 16 min 95 % A.

Method C

Zorbax Eclipse Plus C18 2.1 x 100 mm, 1.8 µ was used as the stationary phase. The eluent was made from the following solvents: 0.2 % formic acid in water (A) and methanol (B). The analysis were performed at the UV max of the compounds (254 nm or 270 nm) to maximize selectivity. The compounds were dissolved in dichloromethane or methanol; the final concentrations were ≈ 1 mg ml^{-1}; the flow rate was 0.2 ml min^{-1}.

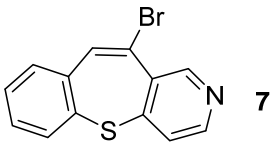
Compounds **14**, **15**, **17**, **18** and **20** were eluted using the gradient protocol: 0 – 0.5 min 95 % A, 0.5 - 3 min 95 % A → 5 % A, 3 - 17 min 5 % A, 17 – 19 min 5 % A → 95 % A, 19 – 20 min 95 % A.

Method D

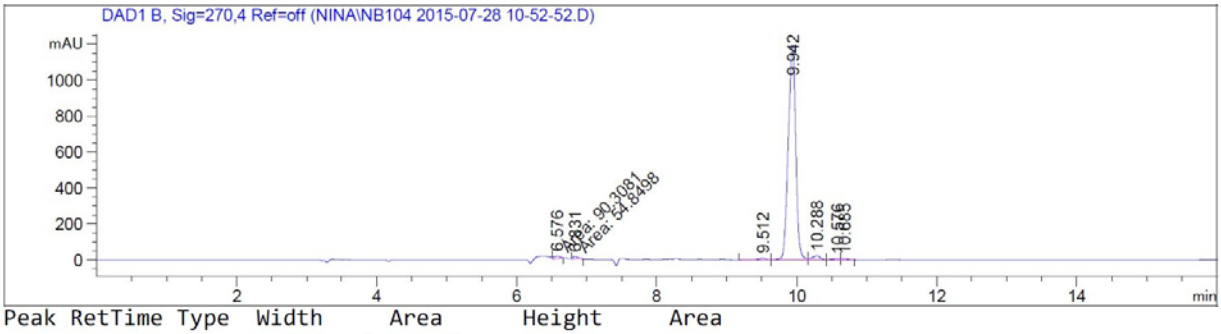
Zorbax Eclipse Plus C18 2.1 x 100 mm, 1.8 µ was used as the stationary phase. Eluent was made from the following solvents: 0.2 % formic acid in water (A) and acetonitrile (B). The analysis were performed at the UV max of the compounds (254 nm or 270 nm) to maximize

selectivity. The compounds were dissolved in dichloromethane or methanol; the final concentrations were ≈ 1 mg ml^{-1}; the flow rate was 0.2 ml min^{-1}.

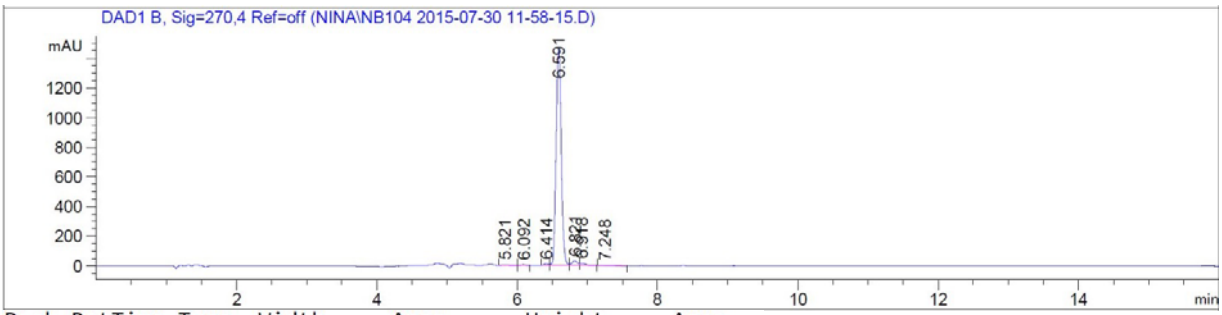
Compounds **14**, **15**, **17**, **18** and **20** were eluted using gradient protocol: 0 – 0.5 min 95 % A, 0.5 - 3 min 95 % A→ 5 % A, 3 - 17 min 5 % A, 17 – 19 min 5 % A→ 95 % A, 19 – 20 min 95 % A.



7

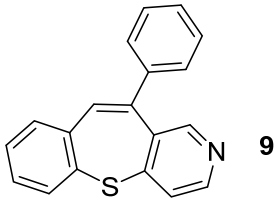


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.576	MM	0.0959	90.30814	15.69702	0.9692
2	6.831	MM	0.0710	54.84978	12.87954	0.5886
3	9.512	BB	0.1078	71.09457	9.23427	0.7630
4	9.942	BV	0.1130	8857.01660	1194.21350	95.0538
5	10.288	VB	0.1106	163.19928	21.98211	1.7515
6	10.576	BV	0.0924	40.86488	5.45643	0.4386
7	10.685	VB	0.0806	40.56753	6.51999	0.4354

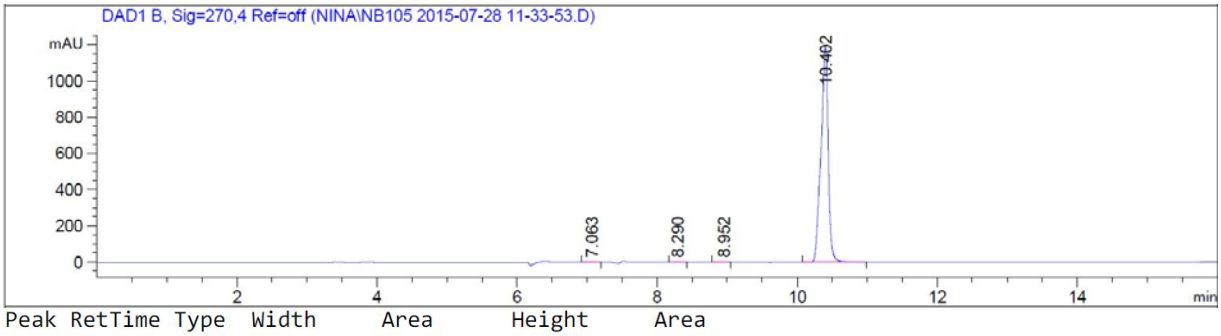


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.821	VV	0.0989	28.89424	3.51626	0.3664
2	6.092	VB	0.0651	27.04103	6.17597	0.3429
3	6.414	BV	0.0649	41.17265	9.83188	0.5220
4	6.591	VV	0.0796	7503.39746	1468.10205	95.1363
5	6.821	VV	0.0889	177.55521	29.22999	2.2512
6	6.918	VB	0.0830	89.33318	16.02348	1.1327
7	7.248	BB	0.1138	19.60444	2.54628	0.2486

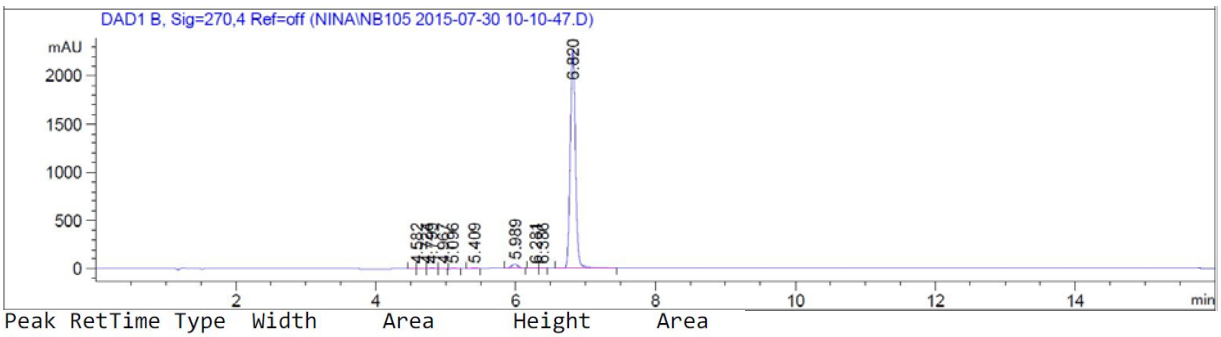
HPLC elution profiles for compound **7**, upper method A and lower method B



9

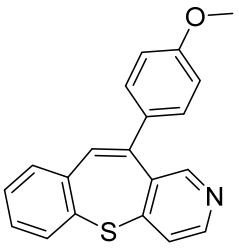


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.063	BB	0.0810	10.16132	1.49043	0.1176
2	8.290	BB	0.0692	11.99468	2.11352	0.1388
3	8.952	BB	0.0894	7.84830	1.05367	0.0908
4	10.402	BB	0.1029	8611.59961	1196.84363	99.6528

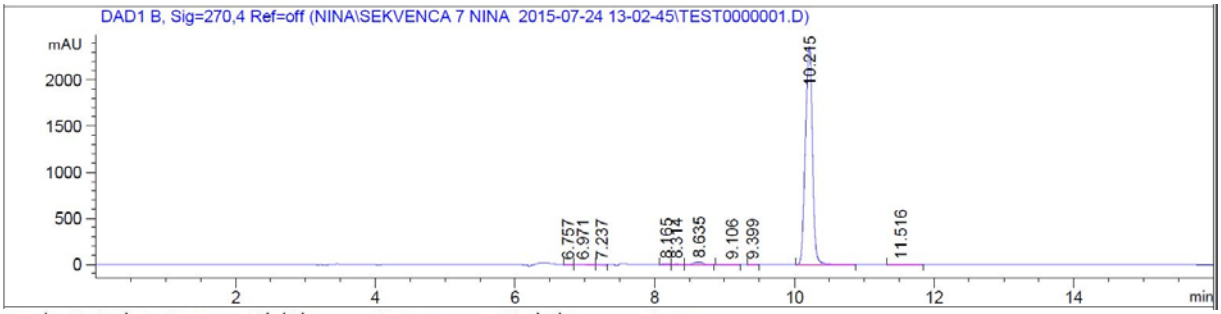


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.582	VV	0.0901	45.13266	5.94333	0.3645
2	4.724	VV	0.0984	52.76317	6.37055	0.4262
3	4.799	VV	0.0948	74.48174	9.43743	0.6016
4	4.967	VB	0.0797	48.46127	7.25762	0.3914
5	5.096	BV	0.0827	50.63825	8.57083	0.4090
6	5.409	BB	0.0558	13.46872	2.89594	0.1088
7	5.989	BB	0.0969	260.16376	40.23710	2.1013
8	6.281	BV	0.0793	8.77044	1.31561	0.0708
9	6.386	VB	0.0556	5.77739	1.24545	0.0467
10	6.820	VV	0.0785	1.18217e4	2271.33203	95.4798

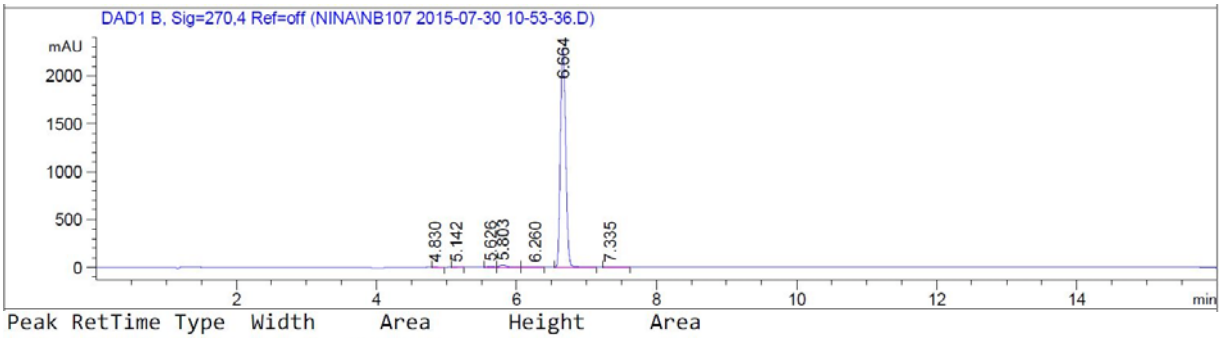
HPLC elution profiles for compound **9**, upper method A and lower method B



10

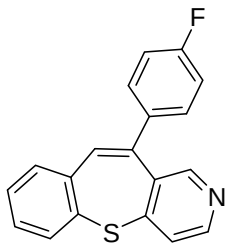


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.757	BV	0.1145	13.58008	1.40229	0.0796
2	6.971	VV	0.1975	108.04030	6.44839	0.6333
3	7.237	VV	0.1217	105.56443	10.33357	0.6188
4	8.165	BV	0.0759	36.92304	7.12745	0.2164
5	8.314	VV	0.0857	18.81927	2.68678	0.1103
6	8.635	VB	0.1138	186.57439	24.50180	1.0936
7	9.106	BB	0.1115	23.38347	2.56277	0.1371
8	9.399	VV	0.0770	9.07039	1.40219	0.0532
9	10.215	BB	0.1126	1.65376e4	2364.83618	96.9390
10	11.516	BB	0.1397	20.24553	1.70851	0.1187

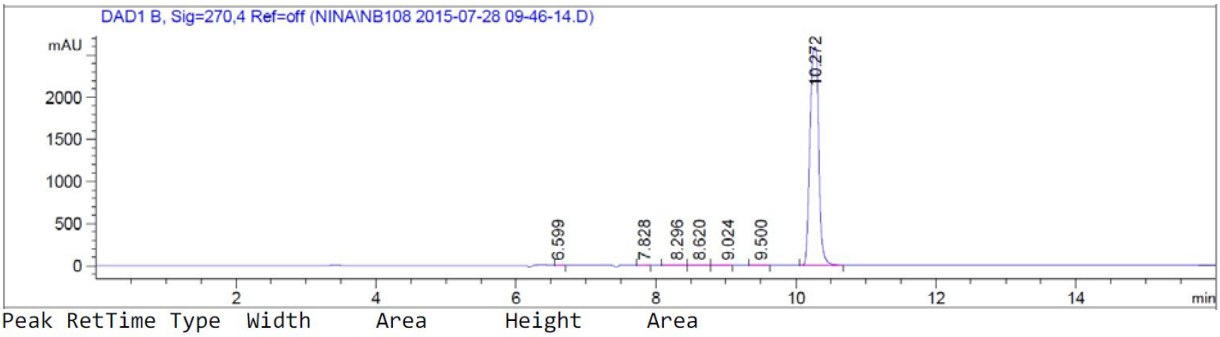


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.830	VB	0.0795	11.91504	1.80633	0.0969
2	5.142	VB	0.0728	18.83530	3.67467	0.1532
3	5.626	BV	0.0798	37.80167	6.85637	0.3075
4	5.803	VB	0.0998	147.77039	23.20591	1.2022
5	6.260	BB	0.1099	30.59805	3.37193	0.2489
6	6.664	VB	0.0833	1.20308e4	2288.28491	97.8794
7	7.335	BB	0.1200	13.73532	1.35751	0.1117

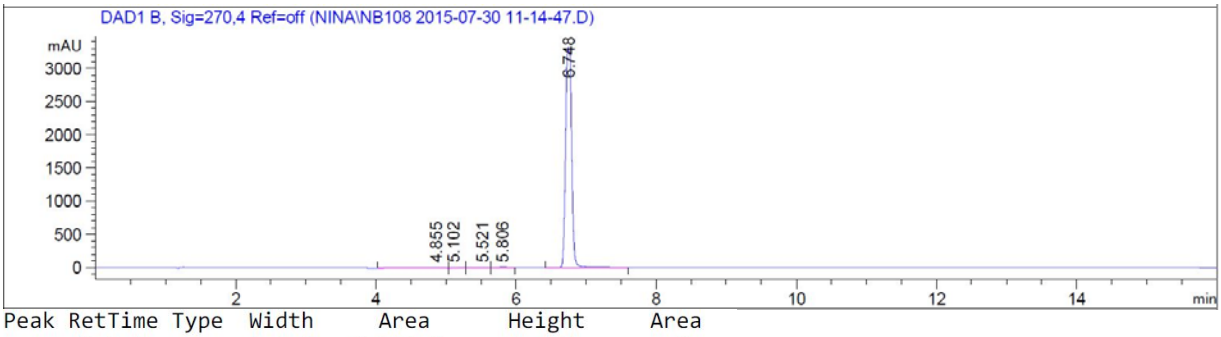
HPLC elution profiles for compound **10**, upper method A and lower method B



11

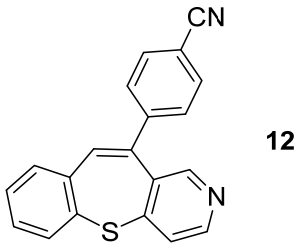


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.599	VB	0.0790	40.39238	6.54809	0.1784
2	7.828	VB	0.1219	37.75359	3.65820	0.1668
3	8.296	BB	0.0815	29.30226	4.46598	0.1294
4	8.620	BB	0.0912	26.41581	3.72610	0.1167
5	9.024	BV	0.1000	10.41194	1.27810	0.0460
6	9.500	VB	0.0763	10.84225	1.76174	0.0479
7	10.272	BB	0.1035	2.24850e4	2596.14014	99.3149

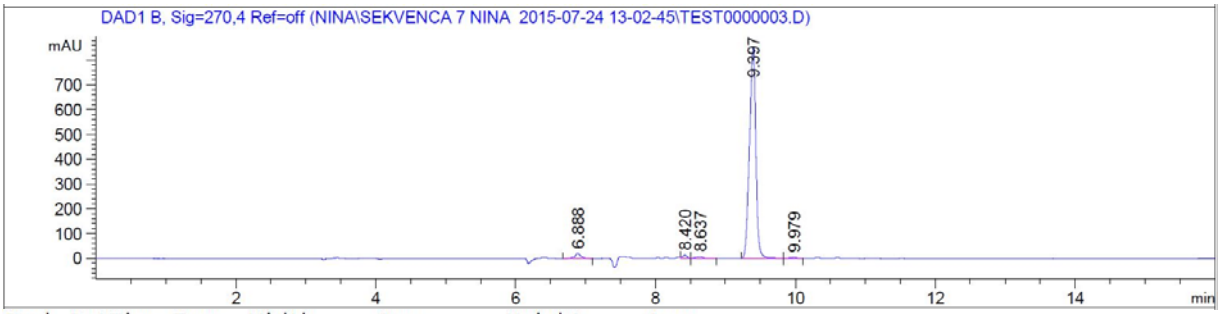


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.855	BB	0.3925	241.60541	7.38788	1.1940
2	5.102	BV	0.1190	70.32722	7.92874	0.3476
3	5.521	VV	0.1999	71.45871	4.31143	0.3532
4	5.806	VB	0.1168	51.57803	5.71265	0.2549
5	6.748	BB	0.0717	1.97992e4	3314.19165	97.8503

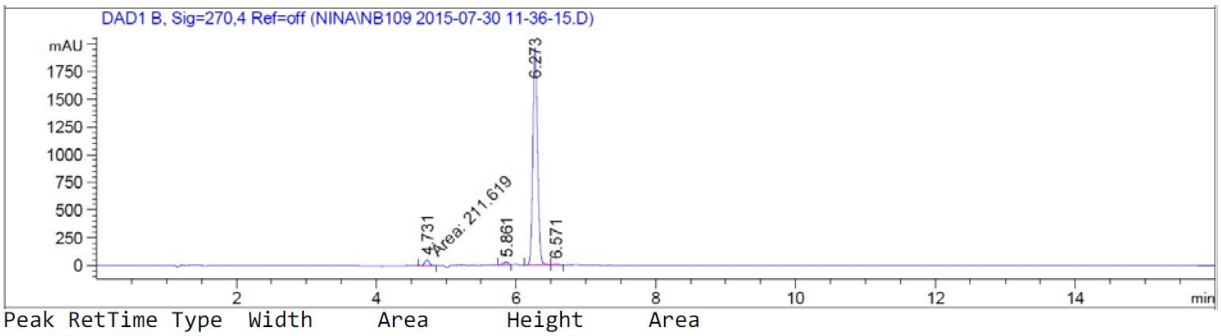
HPLC elution profiles for compound **11**, upper method A and lower method B



12

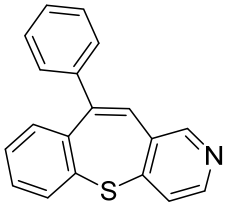


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.888	BB	0.0826	124.82822	20.92245	2.2060
2	8.420	VV	0.0695	60.38920	12.59124	1.0672
3	8.637	VB	0.1036	57.28471	7.41694	1.0124
4	9.397	VV	0.0942	5386.36865	852.95148	95.1895
5	9.979	VB	0.0981	29.70112	4.19751	0.5249

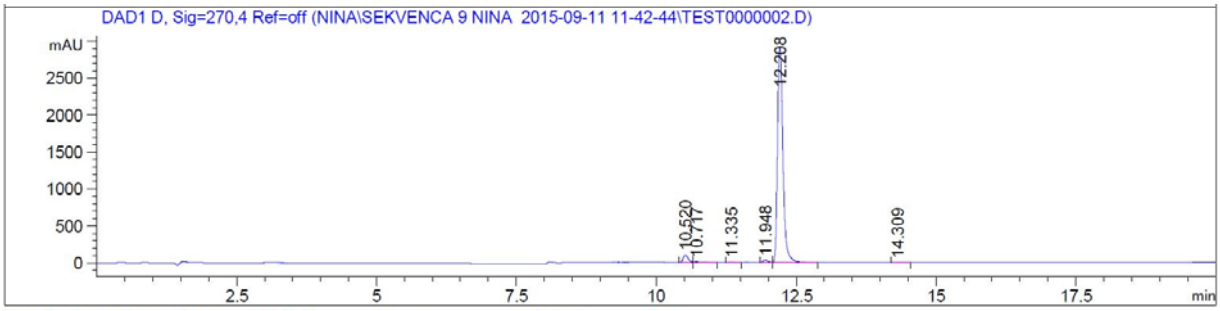


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.731	MM	0.0713	211.61905	49.46984	2.2309
2	5.861	BV	0.0778	152.16524	27.82576	1.6042
3	6.273	BV	0.0710	9068.69238	1959.10767	95.6046
4	6.571	VB	0.0799	53.15163	10.19005	0.5603

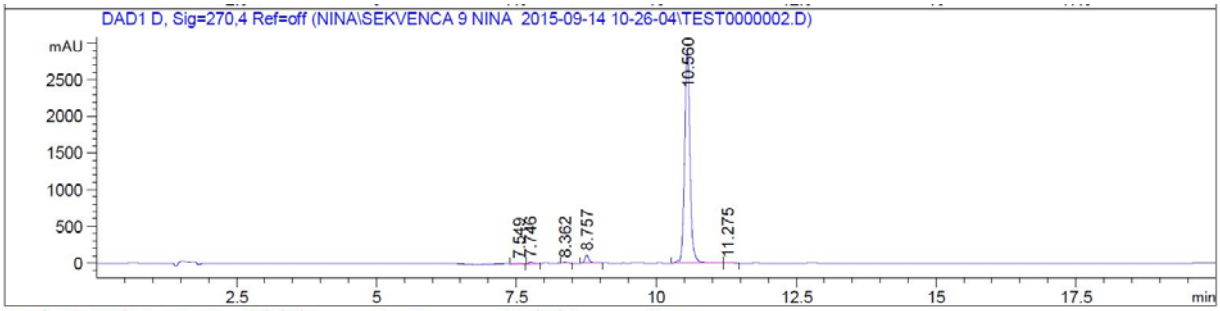
HPLC elution profiles for compound **12**, upper method A and lower method B



14

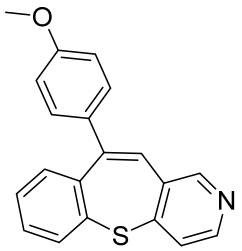


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.520	BV	0.0972	639.78992	103.35240	3.0779
2	10.717	VB	0.1059	76.18915	9.12214	0.3665
3	11.335	VB	0.0867	20.35608	3.17935	0.0979
4	11.948	BV	0.0975	206.47504	32.54118	0.9933
5	12.208	VB	0.0923	1.98205e4	2916.68823	95.3538
6	14.309	BB	0.0909	22.95485	3.17439	0.1104

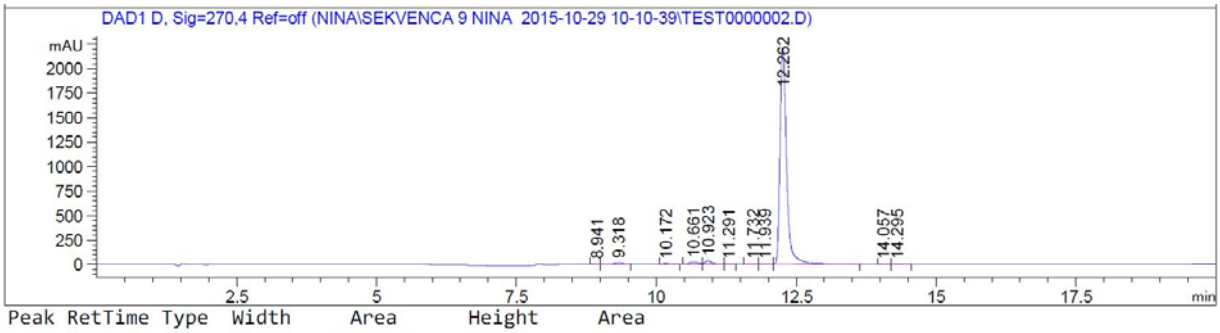


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.549	VB	0.1609	133.01857	9.86188	0.6552
2	7.746	BB	0.0768	104.59921	19.89641	0.5152
3	8.362	VV	0.0793	45.45561	8.44947	0.2239
4	8.757	BV	0.0811	578.63983	109.66137	2.8503
5	10.560	BV	0.0794	1.94261e4	2929.59204	95.6911
6	11.275	VB	0.0812	13.03478	1.90850	0.0642

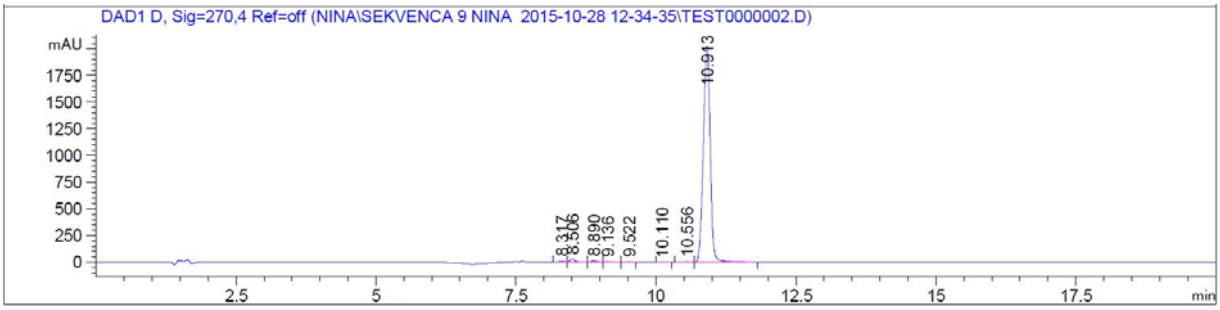
HPLC elution profiles for compound **14**, upper method C and lower method D



15

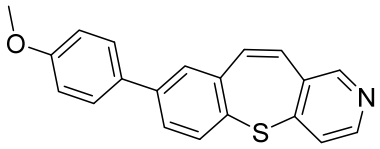


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.941	VV	0.1202	32.72911	3.21556	0.1751
2	9.318	VV	0.1373	152.35715	13.96070	0.8152
3	10.172	BB	0.0926	28.81367	3.97153	0.1542
4	10.661	BV	0.1304	172.19441	17.71878	0.9213
5	10.923	VV	0.1198	251.42107	31.26252	1.3452
6	11.291	VB	0.0784	11.15880	1.68200	0.0597
7	11.732	BV	0.0905	29.08542	3.88005	0.1556
8	11.939	VV	0.1164	30.09163	3.05655	0.1610
9	12.262	VB	0.1238	1.79622e4	2210.71948	96.1070
10	14.057	BV	0.1047	9.39958	1.06275	0.0503
11	14.295	VB	0.1200	10.34390	1.04072	0.0553

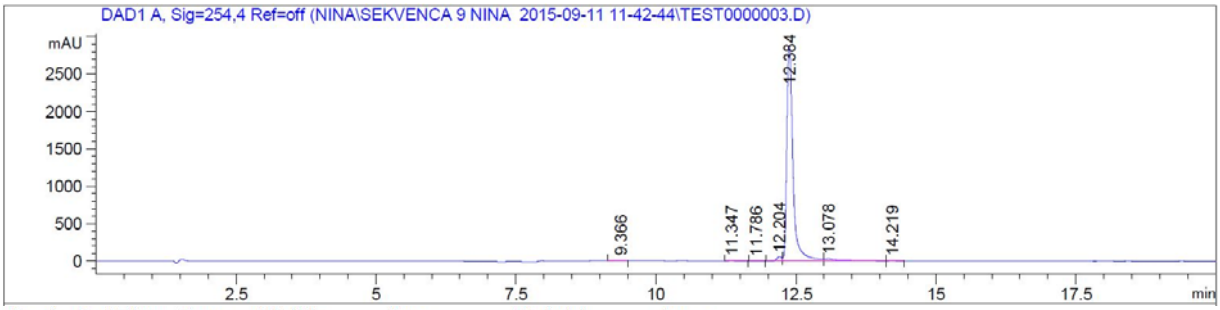


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.317	BV	0.0877	73.94875	12.03510	0.4154
2	8.506	VB	0.0942	187.72165	30.53401	1.0544
3	8.890	BV	0.1023	103.37145	14.39678	0.5806
4	9.136	VB	0.0980	30.32004	3.90892	0.1703
5	9.522	BB	0.0776	19.10745	2.94751	0.1073
6	10.110	BB	0.0789	18.27873	2.81075	0.1027
7	10.556	BB	0.0840	23.72359	3.37404	0.1333
8	10.913	BB	0.1330	1.73473e4	2024.83496	97.4361

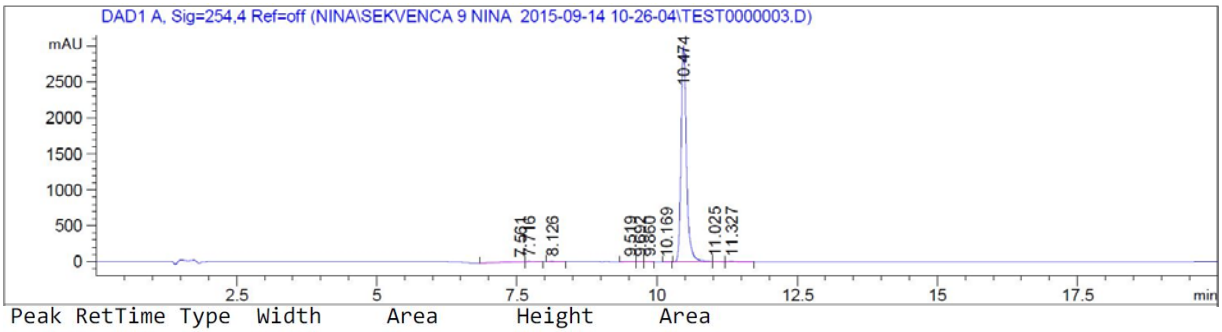
HPLC elution profiles for compound **15**, upper method C and lower method



17

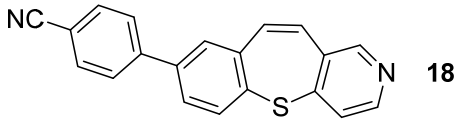


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.366	BV	0.1353	12.97182	1.15296	0.0555
2	11.347	BB	0.1142	44.75092	5.72373	0.1915
3	11.786	BB	0.0883	12.53788	1.68475	0.0537
4	12.204	BV	0.0908	336.30023	57.87526	1.4391
5	12.384	VV	0.0918	2.22633e4	2891.74512	95.2718
6	13.078	VB	0.2712	667.29565	31.61833	2.8556
7	14.219	BB	0.0965	31.04912	3.81115	0.1329

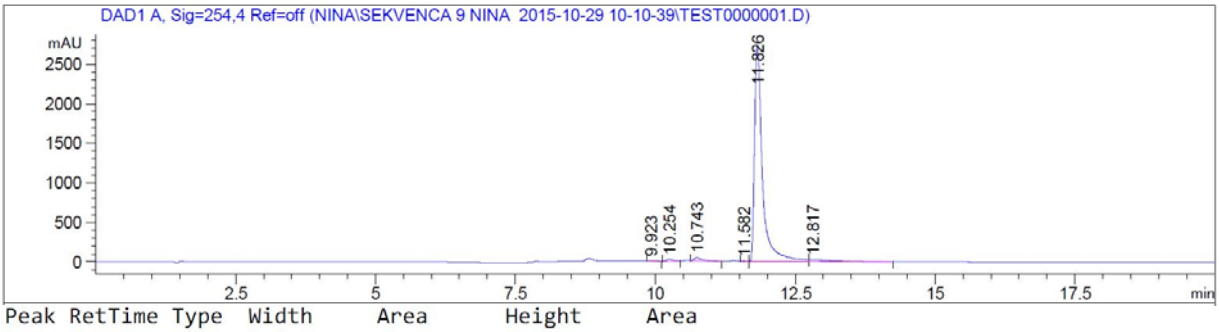


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.561	BB	0.3611	228.75266	7.62266	1.0879
2	7.716	BB	0.0905	91.60204	14.05607	0.4356
3	8.126	BB	0.0872	52.91157	9.11221	0.2516
4	9.519	BV	0.0955	37.20607	5.35729	0.1769
5	9.692	VV	0.0732	21.58880	4.21589	0.1027
6	9.860	VB	0.0793	13.60892	2.16578	0.0647
7	10.169	BB	0.0657	7.50022	1.47720	0.0357
8	10.474	BV	0.0838	2.04148e4	3003.15430	97.0852
9	11.025	VV	0.0998	60.92194	7.82446	0.2897
10	11.327	VB	0.1053	98.82442	13.59944	0.4700

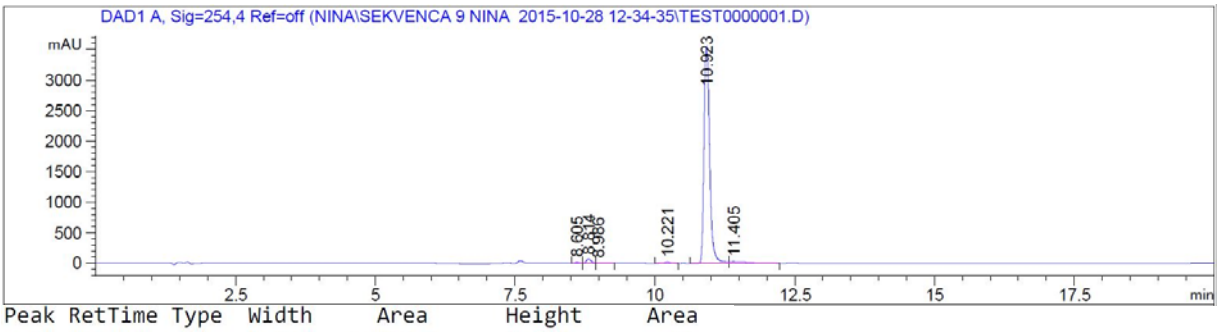
HPLC elution profiles for compound **17**, upper method C and lower method D



18

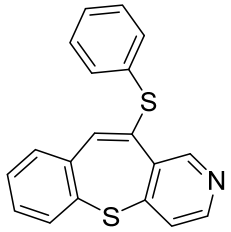


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.923	VB	0.1100	23.65680	2.55436	0.0839
2	10.254	BB	0.1140	165.78282	22.35710	0.5879
3	10.743	VB	0.1385	437.65625	45.17911	1.5521
4	11.582	VB	0.0719	15.14873	2.54779	0.0537
5	11.826	BV	0.1431	2.68186e4	2729.18677	95.1073
6	12.817	VB	0.3435	737.40631	25.48751	2.6151

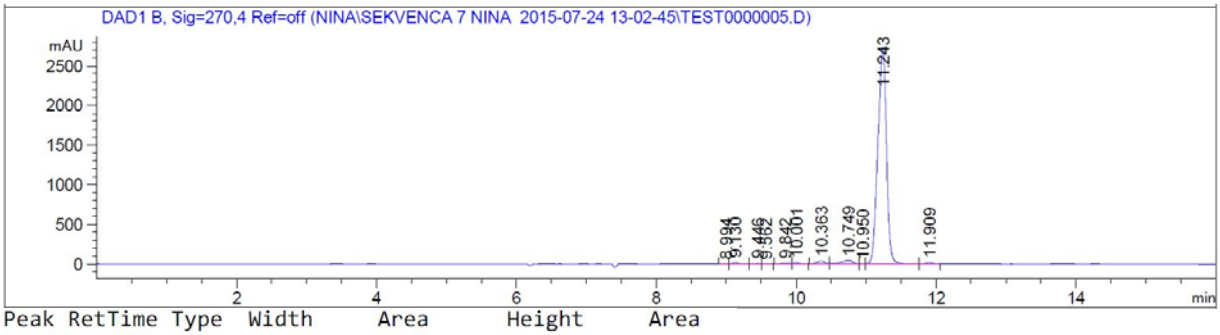


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.605	BV	0.0856	81.16890	14.66023	0.3092
2	8.814	VV	0.0957	396.13065	64.47784	1.5088
3	8.986	VB	0.0932	49.25348	6.94456	0.1876
4	10.221	BV	0.1060	143.40079	19.79706	0.5462
5	10.923	BV	0.0860	2.49882e4	3553.27563	95.1753
6	11.405	VB	0.2800	596.76550	25.98180	2.2730

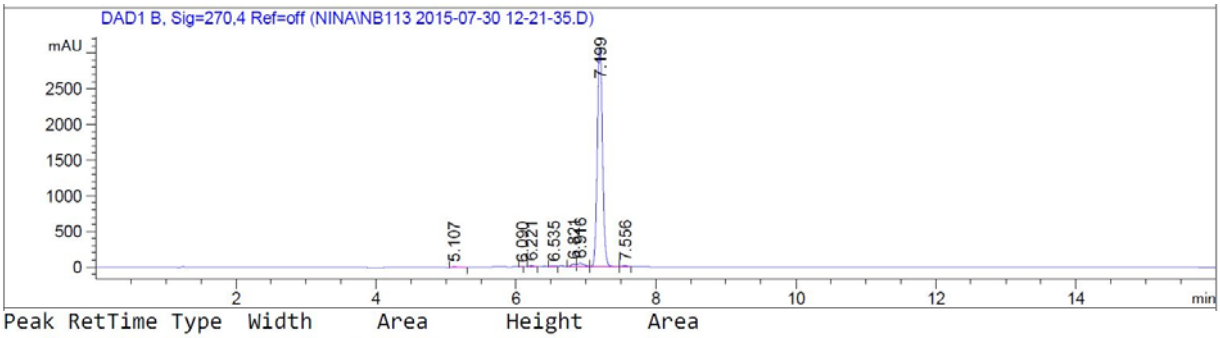
HPLC elution profiles for compound **18**, upper method C and lower method D



19

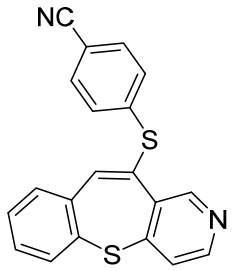


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.994	BV	0.0637	19.01350	4.08923	0.0778
2	9.130	VB	0.0831	77.64167	13.30229	0.3176
3	9.446	BV	0.0743	29.46633	4.82399	0.1205
4	9.562	VB	0.0708	24.73343	4.22413	0.1012
5	9.842	BV	0.1091	84.75491	10.02737	0.3467
6	10.001	VB	0.0929	77.84397	12.21028	0.3184
7	10.363	BV	0.1162	262.28683	33.73746	1.0728
8	10.749	VV	0.1749	477.60129	42.55501	1.9534
9	10.950	VV	0.0680	18.32907	3.71904	0.0750
10	11.243	VB	0.1290	2.32843e4	2731.29443	95.2355
11	11.909	BB	0.1013	93.22077	13.38474	0.3813



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.107	BV	0.1371	108.18636	10.20858	0.6448
2	6.090	BV	0.0357	5.25130	1.93432	0.0313
3	6.221	VB	0.0562	55.25375	14.93462	0.3293
4	6.535	BV	0.0730	47.25948	10.30827	0.2817
5	6.821	BV	0.0654	175.72183	40.65167	1.0473
6	6.916	VV	0.0917	330.94272	50.35007	1.9725
7	7.199	VV	0.0800	1.59925e4	3060.41846	95.3179
8	7.556	VB	0.0686	62.94118	14.22441	0.3751

HPLC elution profiles for compound **19**, upper method A and lower method B



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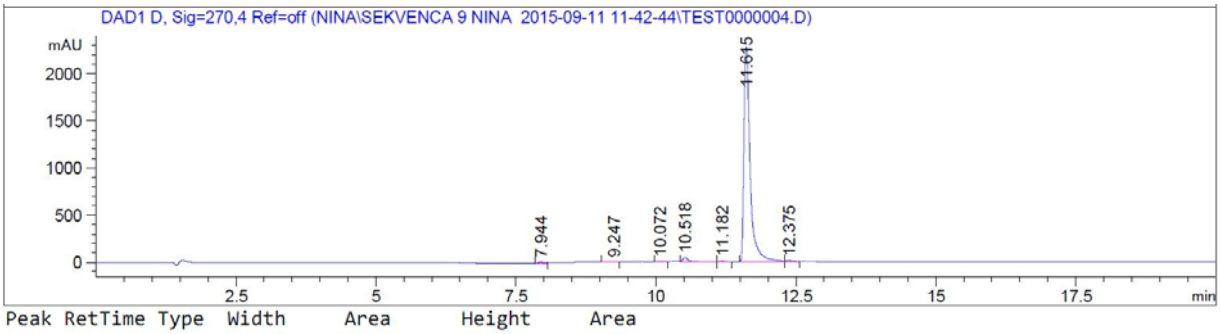
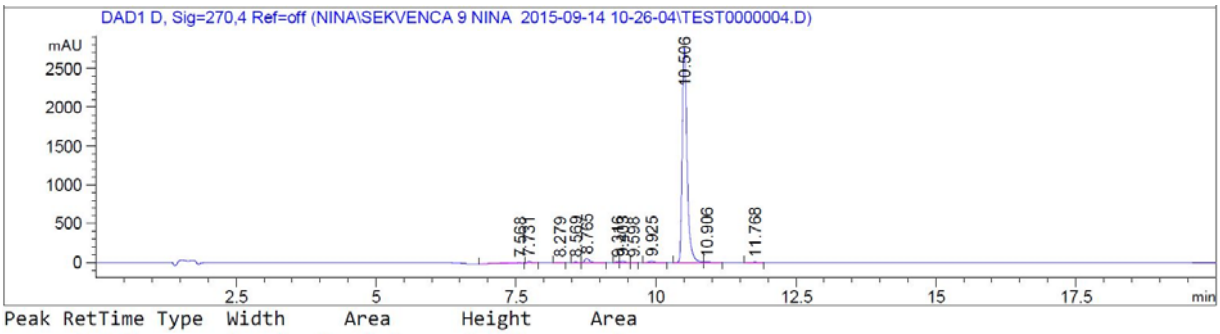
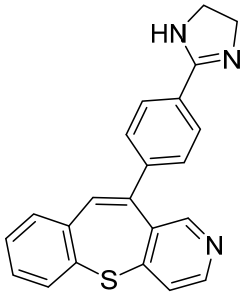


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.944	BV	0.1108	108.96072	14.15138	0.5971
2	9.247	VB	0.2564	31.30817	1.43606	0.1716
3	10.072	BB	0.0741	20.72905	3.40249	0.1136
4	10.518	VB	0.1059	302.83405	43.94425	1.6596
5	11.182	BV	0.0938	53.69085	8.15767	0.2942
6	11.615	BV	0.1155	1.75450e4	2275.54712	96.1533
7	12.375	VV	0.1403	184.38396	16.64104	1.0105



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.568	BB	0.3969	237.89294	7.03718	1.3572
2	7.731	BB	0.0748	84.00637	16.38684	0.4793
3	8.279	VV	0.0934	10.96703	1.39296	0.0626
4	8.569	BV	0.0695	19.37259	3.99965	0.1105
5	8.765	VV	0.0842	258.00977	46.88646	1.4720
6	9.316	BV	0.0546	22.99936	6.08250	0.1312
7	9.403	VV	0.0811	60.06289	10.76114	0.3427
8	9.598	VB	0.0644	8.58380	1.96720	0.0490
9	9.925	VB	0.0952	74.67310	11.13384	0.4260
10	10.506	BV	0.0911	1.66782e4	2776.06665	95.1509
11	10.906	VV	0.1015	50.78512	6.61984	0.2897
12	11.768	BB	0.0760	22.60033	3.61177	0.1289

HPLC elution profiles for compound **20**, upper method C and lower method D



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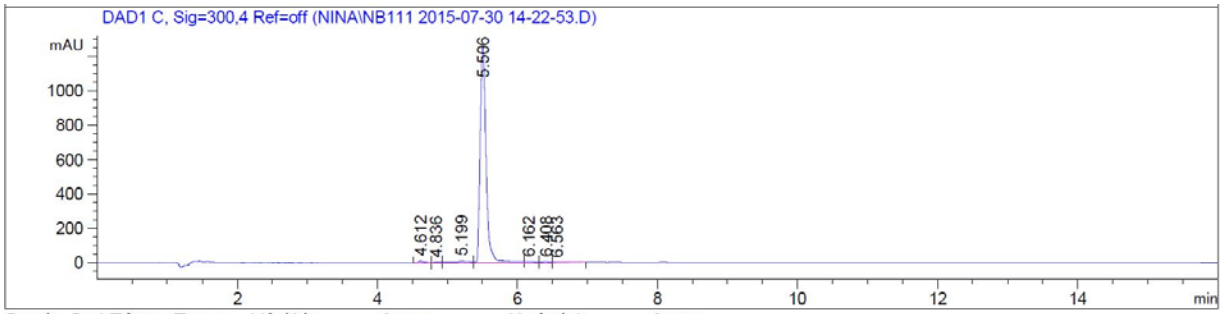
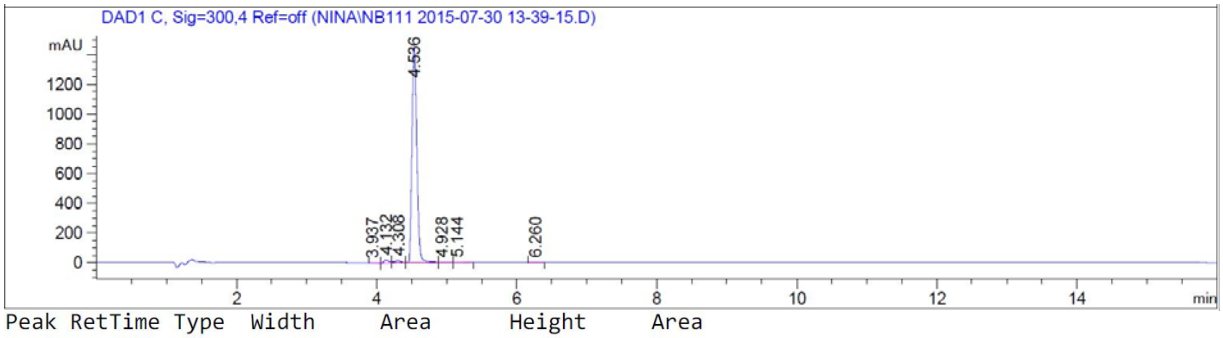


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.612	BB	0.0757	56.75945	10.63887	0.7516
2	4.836	BV	0.0700	13.15713	2.30685	0.1742
3	5.199	VV	0.1460	95.34753	8.36601	1.2626
4	5.506	VV	0.0890	7285.84912	1250.28284	96.4829
5	6.162	VV	0.1297	43.96879	4.26788	0.5823
6	6.408	VV	0.1012	30.50436	3.66132	0.4040
7	6.563	VB	0.1427	25.85148	2.25607	0.3423



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.937	BB	0.0631	6.39481	1.30638	0.0873
2	4.132	BV	0.0738	108.18619	21.29767	1.4776
3	4.308	VV	0.0951	117.23798	17.07328	1.6012
4	4.536	VV	0.0755	7028.17334	1452.48560	95.9883
5	4.928	VV	0.1118	33.59949	3.72330	0.4589
6	5.144	VB	0.1044	22.40838	2.71325	0.3060
7	6.260	BB	0.0633	5.90258	1.15082	0.0806

HPLC elution profiles for compound **21**, upper method A and lower method B